HPRA
An t Údarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Roisin Hickey,
Quality Assurance Director,
Hovione Limited,
Loughbeg,
Ringaskiddy,
Co. Cork.

Manufacturer's Authorisation No: M11208
Investigational Medicinal Products Manufacturer's Authorisation No: M11207
Active Substance Registration No: ASR11447

27th May 2015

RE: Inspection Reference: 9335

Dear Ms. Hickey,

We would like to convey our thanks to you and to the personnel of Hovione Limited for the co-operation extended to us during the inspection on the 11th – 15th May 2015.

Please find enclosed the report for the inspection. If you wish to make comments on the content of the report please forward these with the response to the deficiencies.

The objective of the inspection was to determine compliance of manufacturing operations with Part I and Part II of the EU Guide to Good Manufacturing Practice (GMP).

The level of compliance of the company's facilities and operations with the principles of GMP was, in general, considered to be satisfactory.

Many compliances with the requirements of current GMP were observed during the inspection. However this report details only the non-compliances with GMP and any other specific issues of note.

It is possible that not all non-compliances that exist were identified during the course of the inspection.

The company is requested to reply to the deficiencies / clarifications outlined by the 19th June 2015.

For deficiencies the format of the reply should be as follows:
(i) Restate the deficiency cited by the HPRA;
(ii) Include, if necessary, any comment which the company considers to be appropriate;
(iii) State proposed /actual corrective action(s) relating to the individual deficiency;
(iv) State target date(s) for completion of the corrective action(s).

It is not considered necessary for all issues to have been completed by the due date for reply, rather that the company submit a response to this inspection report by the date identified, defining the target completion dates for those issues. The HPRA will then confirm if the proposed corrective actions and timescales are considered to be acceptable.

Please do not hesitate to contact us if you have any issues with the content of the report that require clarification.

We look forward to hearing from you.

Yours sincerely,

Catherine Neary
Inspector

Alfred Hunt
Inspector

HPRA

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Health Products Regulatory Authority

GMP INSPECTION REPORT

Report Reference No:	9335
Inspected Site(s):	Hovione Limited Loughbeg Ringaskiddy Co. Cork Ireland
Activities Carried Out:	Manufacture and Importation of Active Substances; Manufacture of an Excipient; Manufacture of Intermediates.
Inspection Date(s):	11 – 15 May 2015
Inspector(s):	Catherine Neary Alfred Hunt
References:	Manufacturer's Authorisation No.: M11208 Investigational Medicinal Products Manufacturer's Authorisation No.: IMP11207 Active Substance Registration No.: ASR11447

Introduction

Hovione Limited was a contract manufacturing organisation, located on a large scale commercial manufacturing site (area of 115,461m^2) 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. The company supplied its products to Europe (24% sales), North America (52% sales), Japan (13% sales) and Rest of World (11% sales).

Date of Previous Inspection

22 – 23 April 2015 (non-routine inspection)
11 July 2014 (non-routine inspection)
5 – 8 February 2013 (routine inspection)

Inspectors on Previous Inspection
Chris Cullen & Victor Garvin (non-routine inspection April 2015)
Victor Garvin (non-routine inspection July 2014)
Victor Garvin & Paul Moody (routine inspection February 2013)

Major Changes since Previous Inspection

- A number of changes to key personnel including the General Manager, Director of Quality, Director of Engineering, Director of Finance/Supply Chain/IT and Qualified Persons (QPs) had occurred in the period since the last routine inspection
- A number of new instruments had been purchased for the laboratory and included the following:- FTIR, UPLC, Refractometer, Particle size analyser, Milli-Q water system

Future Planned Changes
An automation upgrade high level plan was in place for the period 2015 - 2019 which included a number of hardware and software upgrades in the manufacturing facilities in Building 01 (B01) and Building 10 (B10). A plan for the introduction of new equipment to the site for the period 2015 - 2016 was also in place. Future investment in utilities/facilities was under assessment at the time of the inspection.

Brief Report of the Inspection Activities Undertaken:

Scope of Inspection:
The objective of the inspection was to determine compliance of manufacturing operations with Part I and Part II of the EU Guide to Good Manufacturing Practice (GMP).

Inspected Area(s):

Quality Management
Deviations
Quality Risk Management
Internal Audits (Self-Inspection)
Product Quality Review

Personnel
Personnel Hygiene

Buildings and Facilities
Design and Construction
Utilities
Water
Containment
Sanitation and Maintenance

Process Equipment
Design and Construction
Equipment Maintenance and Cleaning
Computerized Systems

Documentation and Records
Documentation System and Specifications

Equipment Cleaning and Use Record
Batch Production Records (Batch Production and Control Records)
Laboratory Control Records

Materials Management
General Controls
Receipt and Quarantine
Sampling and Testing of Incoming Production Materials
Storage
Re-evaluation

Production and In-Process Controls
Production Operations
Time Limits
In-process Sampling and Controls
Blending Batches of Intermediates or APIs
Contamination Control

Packaging and Identification Labelling of APIs and Intermediates
General
Packaging Materials
Label Issuance and Control
Packaging and Labelling Operations

Storage and Distribution
Warehousing Procedures
Distribution Procedures

Laboratory Controls
General Controls
Testing of Intermediates and APIs
Stability Monitoring of APIs
Expiry and Retest Dating
Reserve/Retention Samples

Validation
Validation Policy
Validation Documentation
Process Validation

Change Control

Rejection and Reuse of Materials
Rejection
Reprocessing
Reworking
Recovery of Materials and Solvents
Returns

Complaints and Recalls

Contract Manufacturers (including Laboratories)

Agents, Brokers, Traders, Distributors, Repackers, and Relabellers
Not Applicable

Specific Guidance for APIs Manufactured by Cell Culture/Fermentation
Not Applicable.

APIs for Use in Clinical Trials
Not Applicable.

Activities not Inspected
Personnel – Job descriptions, training records, training/hygiene procedures
Process Equipment – Calibration, Maintenance
Validation – Validation master plan, periodic review of validated systems, cleaning validation, validation of analytical methods, qualification of equipment
Storage and Distribution – Distribution of product via air transport

Personnel met during the Inspection:
Refer to Annex 1.

Inspector's Findings and Observations:

Findings and Observations

Quality Management

The company's quality management system (QMS) consisted of Corporate Operating Procedures (Policies), Site Operating Procedures, Internal Operating Procedures and other Work Documents. A number of IT Management Tools had been implemented at the site including a document management system called 'Doc Stream' and a specification control system called 'CDOC'. SAP, LIMS, 'CAPA', 'ChangeStream', 'TrainStream' and 'NavStream' were also implemented. It was explained that the 'NavStream' was an information sharing system to which customers had access to information relating to its own specific products.

The procedure for deviation management (HQ.CCO.COP014.10EP) was reviewed as were deviation numbers 25241, 25289, 25821, 25938, 28054, 28722, 30578, 31629, 33020, 37255, 38655, 38738, 37476, 39505 and 40015. It was considered that deviation investigations and risk assessments conducted were comprehensive and those reviewed during the inspection were considered in general to be satisfactory.

The internal audit schedules for the periods April 2014 – March 2015 and April 2015 – March 2016 were reviewed and compliance with the schedule was found to be satisfactory. It was observed that a standalone audit of 'Data Integrity' had been included and was scheduled for May 2015. It was also observed that an additional standalone audit of 'Contractors' had been added to the 2014 schedule. It was explained that actions arising from internal audits were captured and tracked to completion through the CAPA system.

The site had been inspected by the MFDS (South Korea Ministry of Food and Drug Safety) in April 2015 and by the US FDA in July 2014.

The company's manufacturer's authorisations and Active Substance Registration were reviewed for accuracy and a point to note is included in the report in this regard.

The product quality review documents for product for 2013 and 2012 (covering 1st April to 31st March of relevant years) were reviewed and were considered to be satisfactory.

Personnel

135 personnel were employed at the site at the time of the inspection. Personnel from all areas met by the inspectors were found to be very knowledgeable and competent in their respective areas of expertise. Responsibilities of key personnel were documented in job descriptions; these were not reviewed during the inspection. It was stated that 25-35 contractors were engaged at the site at the time of the inspection, primarily in the Engineering and HSE (Health, Safety & Environment) functions, for the conduction of specialised maintenance activities.

In the production facilities personnel were observed to wear appropriate protective clothing suitable for the manufacturing activities in which they were involved.

Procedures covering hygiene and training requirements and training records were not reviewed during this inspection.

Buildings and Facilities

Buildings B01 (active substance manufacturing), B4 (active substance Glatt drying), B10 (spray-drying facilities), the tank farm, drum store and the warehouse were inspected. The site and buildings in general were observed to be well maintained. Some deficiencies were identified and are included in the report.

The cold storage room (designated as Fridge 4000) was inspected. This fridge was used to store the product (in process material, finished API, previously tested stability samples and retain samples) along with other raw materials requiring low temperature storage. The condition of the fridge was not deemed to be satisfactory as mould was observed to be growing on the walls and ceiling and particles and paint chippings were observed on the floor. A deficiency was issued relating to this. The fridge had two temperature monitors located within. Fridge 3000 was also inspected. At the time of the inspection the fridge was used as an ambient temperature, controlled humidity area for the storage of product which required storage at a relative humidity of less than 65%RH and temperature of less than 25 °C. A dehumidifier unit was located within the room and a temperature and humidity mapping study had been performed during winter months (November 2013). A re-mapping study had not been performed during summer months to assess the potential for seasonal variations within the room and this was identified as a deficiency.

The sampling booth (BT-23-06-1000) located within the warehouse was inspected. The booth was labelled as cleaned and sanitised (a higher level of cleaning); however powder and other particles were observed within the room. The procedure relating to the use and cleaning of the room (HE.WH.IOP.036.8.EN) stated that the sanitisation of the room was valid for 24 hours following completion of the sanitisation. The electronic logbook for the room however, showed that the sanitisation was logged as being completed over five days. Therefore, it was not possible to establish where the 24 hours should be calculated from as the actual sanitisation event (i.e. wiping down with IPA wipes and sanitising agent) could have been conducted at the start or end of the five day period. A deficiency was issued relating to the cleaning and sanitisation of the booth.

The main chemical warehouse (designated as building 23) was inspected. The condition of the warehouse and controls in place within were in general, considered to be satisfactory.

Building 04 and the associated cold room outside the building were inspected. The cold room was installed within an aging transport container. The condition of the cold room was deemed to be inadequate in that the door to the cold room was not seated correctly in the frame which resulted in a gap at the base of the door of approximately five centimetres; furthermore the container was rusted at the base and contained large rust holes in the door. These factors would allow for the entrance of rodents and other contaminants into the area where API intermediates were stored prior to drying. Also located within the coldroom were drums of materials which had recently been relabelled as the original labels had become illegible. These drums contained rejected material from batches manufactured over the previous ten years; however they were not adequately labelled as being rejected or not for use and this was raised as a deficiency. Building 04 contained a Glatt dryer dedicated to the drying of material The dryer was labelled as being clean; however a small amount of material from a previous campaign was observed to be located within the dryer. The general condition of the drying room and dryer discharge room were also observed to be in need of repair in a number of areas.

Building B02 was not in use or commissioned for use at the time of the inspection. The company stated it would take approximately two years to restart operations in this building and it had no plans in that regard at the time of the inspection.

There were seven Air Handling Units (AHUs) installed in B10; three of these had been qualified and related to the ground floor facilities (*which included the cone dryer discharge room, spray dryer/bag filter discharge room and the dispensary*) which were classified as 'level 3' clean-room areas. The company's rationale for this related to the increased potential for product exposure in these areas. Environmental monitoring was conducted in these areas during the manufacturing of products which had microbial limits included in their specifications. The other clean-room classifications in the building were stated to be 'level 2H', at rest. A monthly programme for environmental monitoring was in place and the trend analysis report for the period January – December 2014 was reviewed. It was observed that the AHUs were tested once per year by Controlled Environmental Solutions (CES) for temperature, humidity, particle count, air changes and differential pressures. The company stated that its 'Buildings Management System' (BMS) was not considered compliant with the GMP requirements for computerised systems and that temperature and humidity monitoring was conducted separately using handheld calibrated devices and the records were filed with the batch processing records. It was stated that there were plans to upgrade the BMS and to link it with the Delta V system.

There were three water purification plants on-site (one in B01, one in B10 and one decommissioned unit in CB2). The plant in B10 was inspected (Room R116). Purified water was generated through an ozonation and de-ionisation process. In-line ozone meters, along with conductivity and total organic carbon (TOC) were in place and were linked to the site DeltaV system which would isolate all usage points in the event of an out of specification reading being obtained. An ozone sanitisation process for the entire system was conducted every four weeks. A purified water sampling program was in place at numerous points throughout the site. The preventive maintenance schedule for the plant was managed through the site SAP system. The work order for the UV lamp was inspected and found to be satisfactory.

The trend reports for the purified water in B01 and B10 for the period March 2014 – February 2015 were reviewed and were considered in general to be satisfactory.

Nitrogen supplies on-site were provided from a PSA (Pressure Swing Adsorption) nitrogen generation plant with back-up liquid nitrogen tanks which were supplied, maintained and filled by BOC Industrial Gases Ireland.

Process Equipment

The company stated that no new processing equipment had been installed in the period since the previous inspection in 2013.

The equipment in the spray drying facilities in B10 was observed to be in very good condition in general. It was stated that a complete qualification of the equipment in B10 had been conducted at the end of 2013 and that the same was planned for the equipment in B01. No equipment qualification documentation was reviewed during the inspection.

Equipment within the API manufacturing building B01 was also considered to be in good condition and well maintained.

Cleaning of equipment was inspected and a number of deficiencies were identified and are included in the report.

Procedures for calibration of process equipment and calibration records were not reviewed during this inspection as this activity had been inspected by the HPRA during previous inspections at the site conducted in July 2014 and April 2015. Maintenance of process equipment was not inspected.

The qualification and operation of the Empower 3 chromatographic data acquisition system in the laboratory was inspected, the details of which are included in the section below entitled 'Laboratory Controls'.

The company provided access to a number of systems on-site to clients for information purposes through a computerised system called NavStream. A review of this system was performed and it was deemed to provide non-GMP critical information to clients only with all critical information being accessed through validated methods and systems.

Documentation and Records

A number of procedures and records were reviewed and are included in the relevant sections of the inspection report.

Logbooks related to GC15 in the laboratory were reviewed and a point requiring clarification is included in the report in this regard.

A number of pieces of equipment and processing areas labelled during the inspection as being clean were observed to have potential particles / material from previous campaigns in evidence. A number of deficiencies were raised relating to this and are further discussed within the relevant sections of this report.

The specification (GQSP2546.4) for active substance was reviewed as were the laboratory control records for batch for which an out of specification (OOS) result for the residual solvent acetonitrile had been confirmed (OOS 38805).

The batch release and shipping procedure (HE.DQ.SOP135.5.EN) was reviewed and considered, in general, to be satisfactory. An example of a batch processing record for a released batch was inspected. The review and release of this batch was deemed to be satisfactory and involved a comprehensive review by the Qualified Person.

Materials Management

Bulk solvents on-site were stored within a tank farm containing dedicated tanks and lines to production areas. Dedicated flexi-pipes were used for unloading of tankers. All bulk deliveries of solvents on-site were tested by the laboratory prior to charging into the tanks. These samples were taken by warehouse personnel at a single point at the top of the tanker. A deficiency was raised as an assessment had not been performed by the company to determine whether a single location sample was representative of the entire tanker. Routine testing of the contents of bulk tanks was also conducted quarterly. Pressure venting of the tanks was to atmosphere. The company had conducted a study into the potential for cross-contamination

between tanks which was in draft at the time of the inspection. The company were requested to forward this report to the HPRA upon completion.

Solvents were supplied into manifolds within manufacturing areas through dedicated lines. In the event of a changeover of solvent a cleaning protocol was followed, this included purging, cleaning, and flushing of lines. An example of such a record (HE.CLN.PL.0092.1.EN) was inspected and found to be satisfactory.

The status of all production materials on-site (i.e. release, quarantine, reject etc.) was controlled electronically via the SAP system with unique labelling and numerical item identification.

Production and In-Process Controls

There were no manufacturing operations underway in the spray drying facilities in B10 during the week of the inspection. It was stated that a campaign had recently finished over the previous weekend and that the changeover and cleaning operations could take up to 12 days to complete. The product train was walked through during the inspection and the various areas and equipment had either been cleaned or was undergoing cleaning operations at the time. The cleaning protocol (CD-SP-1002) was reviewed and a number of deficiencies were identified and are included in the report.

There were no manufacturing activities underway in the active substance manufacturing facilities in B01 until the final day of the inspection when an inspection of the facility was conducted.

Hold times (time limits) for the active substance intermediate stages were discussed with the company and it was stated that the time limits implemented had been provided by the customer and had never been verified at the site. A process re-validation for this product had been completed during 2014 and verification of the hold times had not been completed as part of that study and this was highlighted as a deficiency.

Potential sources of particulate matter were observed in certain areas in B10 with respect to contamination control and these were identified as deficiencies.

In-process sampling of API was performed by manufacturing personnel with all testing being performed within the QC laboratory.

No batches of finished API or drug product intermediates were blended.

Packaging and Identification Labelling of APIs and Intermediates

The procedures for the packaging and labelling of spray dried intermediates in B10 were described by the company and appeared in general to be satisfactory. No packaging or labelling activities were being conducted at the time of the inspection.

All labelling of APIs and intermediates were controlled by the site SAP system. Labels observed during the inspection were deemed to be satisfactory.

Storage and Distribution

The storage of material on-site was in general, considered to be satisfactory, with a number of deficiencies identified. These issues along with the control of material on-site (raw materials, in-process, finished product etc) is discussed within further sections of this report.

The company distributed the majority of products via air. A customer complaint (Ref: 26121) was reviewed which potentially originated through the changes in air pressure and temperature within the hold cargo; however this was not identified as a likely root cause.

Laboratory Controls

There were four different sections in the laboratory as follows:-

In Process Control & Continuous Release Team - this group included one team leader and eight analysts who worked on a 4 cycle shift and provided 24/7 support for the production operations.

New Product Introduction Team – this group included one team leader and four analytical chemists who were involved in technical transfer and method validation/transfer activities.

Release and Stability Team – this group included one team leader, one stability co-ordinator and eight analysts who were involved in routine analysis for release, stability analysis, raw materials, packaging materials & solvents testing, water testing & management of the environmental monitoring programme.

Instrumentation, Software & Training – this group included two technical specialists, one of which acted as team leader, and one trainer. The technical specialists were responsible for instrument calibration and maintenance and for the various software packages in use for data acquisition purposes. It was stated that the company planned to remove the trainer from this group with the view to this person reporting directly to the Quality Control Director.

Laboratory equipment installed included sixteen HPLCs and eight GCs. A UPLC had been installed in the period since the previous inspection and it was stated that this instrument was not in use for any commercial testing at the time of the inspection. All of the QC chromatographic equipment in use was networked and 'Empower 3' data acquisition software had been implemented at the site in June 2013. It was stated that 'Cerity' software had been implemented at the site prior to that time. The electronic signature function on Empower 3 had not been implemented and the company stated that it planned to implement this at a point in the future. The configuration and operation of Empower was inspected and a number of deficiencies were identified and are included in the report. It was observed that manual integration was used on a routine basis and when this was queried with the company it stated that it had recently raised a change control to address this. This change control (CC7007) was reviewed; it had been raised on the 23rd April 2015 and related to increasing data integrity on Empower. The changes proposed including the locking of the files and the implementation of auto-integration; it proposed that no manual integration was to be permitted unless justified. This change control was undergoing assessment by all sites in the group at the time of the inspection and once the assessment was completed an implementation plan was to be put in place. It was observed that no procedure for the operation of Empower had been implemented until the 11th January 2014 (*QSD.IF.1130*), six months after the initial go-live date and this was identified as a deficiency. Training had been provided by Waters to the system administrator and key users on the 27th February 2013 and on the 6th - 7th March 2013 and user training had been provided to analysts on the 10th May 2013. Change control CC5391 had been raised for the transition from Cerity to Empower and HPLC/GC systems were transitioned over on a phased basis. It was stated that the draft

procedure for operation of Empower was used by the analysts and the procedure had evolved during the initial period and was finalised in January 2014 at the time all systems had been switched over to Empower.

The company had conducted its first periodic review of Empower and the report for this had been approved on the 29th April 2015. The company had conducted an audit trail risk assessment for which a report had been approved on the 6th May 2015. The start date selected for the audit trail assessment, was the 1st April 2014 and not the go-live date of the 28th June 2013. The reason for this was not explained in the documentation presented and the explanation provided at the time of the inspection was that this date coincided with the start of the financial year. During the inspection the company was requested to run the system policy audit trail for the period from the date of implementation in June 2013 to the 1st April 2014; it was observed that a number of changes had been made to the policies outside of the company's change control procedure. A number of deficiencies were identified and are included in the report.

The company stated that it had applied the same audit trail risk assessment process for other software packages implemented in the laboratory and that all had been completed with the exception of the UV which was in progress and which was considered to require replacement. The Empower audit trail risk assessment was the only one reviewed during the inspection.

The procedure for the handling of out of specification (OOS) results (HE.DQ.SOP129.3.EN) was reviewed as were OOS investigation numbers 24947, 25810, 26445, 38125 and 38805. Deficiencies were identified in relation to the procedure and are outlined in the deficiency section of the report.

The stability data summary reports for active substance for studies initiated in the period since the last routine HPRA inspection were reviewed and it was observed that 24-month data was available on one batch and 9-month data was available on three batches which had been subjected to a process re-validation study. It was stated that a retest date of 12-months was specified on Certificates of Analysis for this active substance. It was stated that this active substance was the only one for which the storage of the stability samples was conducted on the site and that storage of other stability samples was contracted out to Lancaster Laboratories in Dungarvan, Co. Waterford.

No analytical method validation or method transfer activities were reviewed during the inspection.

Validation

Concerns had been raised at the time of the previous routine HPRA inspection in 2013 regarding the company's investigation and handling of elevated levels of the residual solvent, acetonitrile, which had been detected in batches of the active substance. At that time, the company had committed to conducting analysis on individual containers of active substance until such time as the manufacturing process had been revalidated. The protocol (HE.QSP.PVP134.0.EN) and summary report (HE.QSR.PV166.0.EN) for the revalidation study were reviewed and deficiencies were identified and are included in the report. It was stated that the analytical method used for the determination of acetonitrile had been optimised (i.e. *more sensitive with an LOQ of 0.0035%w/w compared to an LOQ of 0.018%w/w for the old method*) and revalidated in April 2013 and that this new method had not yet been filed in the regulatory dossier by the customer.

Testing of acetonitrile was conducted on the in-process control (IPC) samples using the new method *(it was stated that the test method for IPC samples was not part of the regulatory filing)* and on the finished product samples using both the new and old methods, with the results from the old method reported as this was the current method in the regulatory filing. The list of OOS reports raised for this active substance in the period since the last HPRA inspection in February 2013 was reviewed and it was observed that two OOS reports had been raised for OOS levels of acetonitrile residual solvent. The first one had been raised in July 2013 (OOS 28013) and the second one had been raised in March 2015 (OOS 38805). OOS 28013 was not reviewed during this inspection. OOS 38805 was reviewed and is referenced in the 'Laboratory Control' section above. A decision had not been taken on the recent batch (HE00215) at the time of the inspection and it remained under QC inspection status. No other OOS reports related to OOS acetonitrile levels had been raised in the period. The other OOS reports raised in the period for this material related to assay, water content and impurities. It was observed that a number of OOS reports had been raised for elevated levels of the impurity in stability batches of API . It was understood by the inspector that this was a manufacturing impurity and not a degradation product and a point requiring clarification is included in the report in this regard. It had been observed during the review of the process validation documentation that 'failure to inert equipment used during the re-crystallisation with Nitrogen generated from liquid Nitrogen may lead to the formation of oxidative impurities' and when queried with the company it was clarified that was the only known oxidative impurity.

Change Control

The procedure for change management (HQ.CCO.COP027.7.EN) was reviewed as were change control requests PdA#5896, PdA#5907, PdA#5884, PdA#5991, PdA#6586, PdA#6597, PdA#6113, PdA#6470, PdA#6121, PdA#6274, PdA#5720, PdA#5826 and PdA#6761. The procedure did not adequately describe the method for ensuring that all tasks required to be completed prior to the change event being realised had been completed pre-change realisation. Within the change controls reviewed it was also not always evident which tasks should be conducted pre-change and which should be post-change and when the approval to progress the change was given and by whom. All changes were processed through the Change Stream system, a bespoke computerised system. All unplanned changes were managed through the site's deviation management system. Classification of changes (major or minor) were proposed by the change initiator and confirmed by the quality department. Major changes required the notification and approval of relevant customers prior to the change being implemented.

Rejection and Reuse of Materials

Listings of returns and rejected materials for the period since the last inspection in February 2013 were reviewed and deficiencies were highlighted. A returned and subsequently rejected batch of active substance was not included in the product quality review for the relevant period and in addition, it was considered that the company did not have an adequate system in place for the identification of returned, rejected, reprocessed and reworked products. A number of different listings for the rejected and returned materials relevant to the period had been presented during the inspection.

A number of batches of material had been reprocessed as part of routine operations in order to validate the reprocessing methods. A number of batches had also been reprocessed in order to address deviations. The site had not reworked any material in the period since the previous inspection.

The procedure on reprocessing, reworking and returned products (HQ.CCO.COP028.1.EN) was reviewed and was in general considered satisfactory. All reworking and reprocessing of materials required both the approval of QA personnel and the approval of the regulatory affairs department (based in Portugal) who were responsible for ensuring the activity was in compliance with the regulatory filings for the product in question.

The company did not recover any solvents.

Complaints and Recalls

The procedure for customer complaints (HE.DQ.SOP170.1.EN) was reviewed as were customer complaints 39982, 40023 and 26121 and were, in general, considered to be satisfactory. All other complaints during the review period were non-product quality related.

Complaint 39982 related to black specks and hair being observed on outer polyethylene bags at the customer site of product A root cause analysis was performed by Hovione and a number of potential causes and preventive actions relating to the area and process for packing product within the site were identified.

Complaint 40023 related to partially opened aluminium bags being observed at a customer site of product These aluminium bags contained a polyethylene bag of product. This complaint had been received on 29th April 2015 and remained open at the time of the inspection.

Complaint 26121 related to split aluminium bags being observed at a customer site of product The primary packaging of the product remained intact. An investigation was performed by Hovione and a number of potential root causes identified relating to on-site issues along with potential issues during transportation. Preventive actions were identified by the company and implemented for that product and expanded out to other products on-site. There was no documentation of further communications with the customer maintained with the complaint and this was identified as a deficiency.

It was stated that no recalls or stock recovery had been conducted in the period since the previous inspection.

Contract Manufacturers (including Laboratories)

No contract manufacturers were engaged by the company. A number of contract laboratories were approved on the company's manufacturer's authorisations. The quality agreement with Lancaster Laboratories, dated the 6th June 2013, and the report for the last audit conducted of this laboratory in January 2013 (Audit ID: 2825), were reviewed and were considered to be satisfactory. The services provided by Lancaster Laboratories included microbiological testing of raw materials, active substances, intermediates, water and environmental monitoring samples and also stability storage facilities.

Distribution and Shipment
Distribution and shipment operations were not covered during this inspection.

Questions Relating to the Assessment of a Marketing Authorisation
Not Applicable.

Other specific issues identified
Not Applicable.

Site Master File
The site master file SMF QSD.SMF001, revision 8, was reviewed prior to the inspection and was considered in general to accurately reflect the operations conducted at the site.

Miscellaneous
Not Applicable.

Annexes Attached
Annex 1 – List of personnel met during the inspection.

List of Deficiencies

I Critical Deficiency

None were identified during the inspection.

II Major Deficiency

None were identified during the inspection.

III Other Deficiency

Quality Management

1. Quality Management was considered deficient in that:-
   - 1.1 With respect to deviation number 26445 which related to a confirmed OOS result for Active Substance at the 12-month stability time-point, it included a statement that there was no potential impact for previously manufactured/under production batches 'since the occurrence had happened in stability analysis' which was not considered justified;
   - 1.2 The management of the change control system was deficient for the following reasons:-
     - 1.2.1 In relation to the procedure entitled 'Change Control' (HQ.CCO.COP027.7.EN):-
       - (i) It did not describe the requirement for all tasks required to be completed to be conducted and documented prior to the change event being implemented;
       - (ii) It did not describe the method for determining and documenting whether a change would have an impact on the regulatory filings for the products affected by the change;
     - 1.2.2 The task related to the change control request PdA#5991 was marked as having been completed before the document had been approved;
     - 1.2.3 A task required to be completed before implementation of the change (i.e. obtaining customer approval for the change) had not been completed before implementation of change control PdA# 6597;
     - 1.2.4 A number of tasks required to be completed before implementation of the change (i.e. confirmation of filter changing, cleaning of lines) had not been completed before implementation of change control PdA# 5826;
   - 1.3 A returned and subsequently rejected batch of was not included in the product quality review for the relevant period;
   - 1.4 The company did not have an adequate documented system in place for the identification of returned, rejected, reprocessed and reworked products.

Reference: EU GMP Guide Part II, Paragraphs 2.12, 2.16, 2.60, 13.11, 13.13 & 13.14

Buildings and Facilities & Process Equipment

2. In relation to buildings, facilities and equipment the following was observed:-
   2.1 In relation to the spray drying facilities in B10:-
      2.1.1 Disassembled equipment parts were observed to be stored directly on the floor (*laid out on sheets of aluminium foil*) in the EKATO room;
      2.1.2 In the spray drier/bag filter discharge room a number of potential sources of particulate matter were observed as follows:-
         (i) Aluminium foil used for insulation purposes on vessel PK-10-07-1700;
         (ii) Holes in the ceiling through which pipe-work extended to the floor above were not smooth / sealed;
         (iii) The seal on the end of the bellow was observed to have been cut to align with its steel cover which meant its sealed smooth surface had been compromised;

   (*It is acknowledged that the company had started addressing the above issues during the week of the inspection*)

   2.2 Management of the cleaning of the warehouse sampling/dispensing booth (BT-23-06-1000) was deficient in that:-
      2.2.1 During the inspection of the room, which was labelled as having been cleaned and sanitised, black particles were observed on the floor and white powder on the table within the room;
      2.2.2 Sanitising of the booth was typically performed over a number of days with the validity of the sanitised status of the room being defined by the company as 24 hours from the completion of the sanitisation event; however it was not possible to establish where the 24 hours should be calculated from as the actual sanitisation event could have been conducted at the start or end of the cleaning process.
      2.2.3 The method for controlling the changeover of sanitising agents on a quarterly basis was not adequately defined in the procedure entitled 'Usage and Cleaning of Warehouse Sampling and Dispensing Booth' (HE.WH.IOP.036.8.EN);

   2.3 Mould was observed to be present on the walls and ceiling of the cold room store used for the storage of the

   2.4 A number of flexible pipes were observed within the warehouse without adequate identification or status labels;

   2.5 A documented assessment had not been performed to ensure that the uncontrolled storage conditions within the warehouse were suitable for the storage of all relevant materials;

   2.6 A summer temperature and humidity mapping study had not been performed on the controlled humidity storage area for the

   2.7 In relation to the standard of cleanliness within Building 4:-
      2.7.1 Mould was observed to be growing on the ceiling above the area where operator air hoods and boots were stored;
      2.7.2 A purified water usage point within the dryer room had a non-free draining coiled pipe attached which would lead to the presence of stagnant water within the pipe;
      2.7.3 A light fitting over the pack-off area in the discharge room where Active Substance was exposed was observed to be rusted;

2.7.4 The floor and ceiling within the discharge room was observed to be in need of repair;

2.8 In relation to the missed qualification of the air handling unit for the cone dryer discharge room within B10 (Room 116):-

2.8.1 A deviation or risk assessment had not been raised for the planned delay of the qualification;

2.8.2 A preventive action had not been raised to address the issue of routine maintenance activities being excluded and not conducted following a delay in the routine schedule;

2.9 Dryer DR-04-09-1000, which was labelled as clean, was observed to have material located on the dryer bag and also on the valve leading from the unit;

2.10 The temperature mapping study performed on the exterior cold room (FR-23-05-2000) did not incorporate all areas used for storage of product (i.e. the area closest to the door of the unit). Furthermore, the door seal was observed to be not seated fully leaving the contents of the container open to the ingress of rodents and contaminants.

Reference: EU GMP Guide, Part I, Chapter 3, Paragraphs 3.9 & 3.10;
EU GMP Guide, Part II, Paragraphs 4.20, 4.70, 5.22, 5.26, 7.34, 7.42 & 10.10

Documentation and Records

3. Procedures and Records were deficient for the following reasons:-

3.1 The cleaning protocol in use in the spray drying facilities in B10 (CD-SP-1002) was not current in that:-

3.1.1 Insufficient record entry sections were present for the first flush post strip down which lead to additional quantity entries recorded by production personnel in spaces outside the designated text boxes;

3.1.2 The required 'verification' signatures were not present for a number of the additional entries mentioned above;

3.1.3 Hand amendments had been made to the equipment areas used to calculate the Maximum Allowable Carry Over (MACO) limits;

(*It is acknowledged that the company had initiated an update to the protocol to address the above issues during the week of the inspection*)

3.2 The OOS/OOT SOP (HE.DQ.SOP129.3.EN) permitted the following which was not considered justified:-

3.2.1 In situations where no assignable cause had been attributed to the laboratory, production or sampling operations, the product could be retested and the average retest result reported as the final result;

3.2.2 In situations similar to that described above and where the original result was a duplicate with one OOS result obtained, the reported result was the average of the retests and the one original non-OOS result.

3.3 The method of approval of suppliers and materials for use in production was deficient in that:-

3.3.1 There were no records to show that quality reviews were routinely performed on TSE statement (HQ.QSP.RF872.0.EN) documents completed by suppliers;

3.3.2 There was no documented approval of the contents of TSE statements on Supplier Approval/Qualification Forms (HQ.QSD.RF083.13.EN);

3.3.3 The manufacturer's addresses for all GMP related materials were not included on SAP or on an Approved Supplier List.

Reference: EU GMP Guide, Part I, Chapter 4, Principle & Paragraphs 4.1, 4.2, 4.4, 4.5, 4.6 & 4.29; EU GMP Guide, Part II, Paragraph 6.30

Laboratory Controls

4. Quality control operations were considered deficient in that:-
   - 4.1 The company had not assessed whether samples taken at only a single point within bulk solvent tankers were representative of the entire contents;
   - 4.2 Procedures did not require electronic data to be reviewed during approval of analytical data including HPLC/GC [*the procedure (HE.QC.IOP097.4.EN) stated that the software system can be 'consulted, when required'*];
   - 4.3 With respect to Empower 3:-
     - 4.3.1 It was not clear why some GxP settings were not activated for the system policies (*e.g. 'Dont allow users to copy from non FAT projects to FAT projects*);
     - 4.3.2 The number of entry attempts permitted prior to system lock out was not defined or activated;
     - 4.3.3. The configuration settings for system policies had not been defined at the time of the software installation in June 2013 and details of the settings were not available in the documentation of the initial qualification;
       (*It is acknowledged that the company had taken steps during the week of the inspection to address this matter and had raised deviation number 40331 in this regard*)
     - 4.3.4. No procedure for the operation of Empower had been implemented until the 11th January 2014 (*QSD.IF.1130*), six months after the initial go-live date;
     - 4.3.5. The access group 'Chemist' had been deleted on the 16th April 2015 outside of the company's change control procedure;
     - 4.3.6. A number of changes had been made to the system policies in the period since installation outside of the company's change control procedure (*It is acknowledged that the company conducted an investigation into these changes during the week of the inspection and had raised deviation number 40331 in this regard*);
     - 4.3.7. Regarding the company's first periodic review of Empower approved on the 29th April 2015, there was no supporting documentation to verify the output of the deviation and change control searches conducted for the relevant period (*It is acknowledged that the company had addressed this matter during the week of the inspection and stated that this information would be included as an annex to the report*);
     - 4.3.8. Regarding the company's audit trail risk assessment which had been approved on the 6th May 2015, the following was observed:-
       - (i) No consideration had been given to whether routine review of any item should be conducted every time an analysis is reviewed and approved *(The options had been pre-defined as no review required, 6-month review or 1-year review*);

(ii) The reason the start date of 1st April 2014 was selected and not the go-live date of 28th June 2013, was not explained in the documentation and the explanation provided at the time of the inspection (*i.e. start of financial year*) was not considered to be justified;

(iii) The classification of 'aborted injections' and 'aborted sample sets' as 'low risk' was not considered to be justified;

(iv) The 1-year period review proposed for 'altered samples' (*a privilege granted to analysts*) based on a high probability of detection was not considered to be justified due to the company's current process for data review which did not include a mandatory review of electronic data;

(v) A number of entries which related to 'LDAP Domain Information Changed' had been executed by 'System/Administrator' user and was not traceable to any individual (e.g. on 17.10.14 x 2, 05.02.15, 11.02.15 & 26.03.15). In addition, these changes had not been progressed through change control and the implications of the changes were not documented under the quality system at the time of the inspection;

4.3.9. Regarding the system policy audit trail review for the period not covered by the company's risk assessment (*i.e. from date of installation to 01.04.2014*) it was observed that there were no explanations for a number of changes which had been made and which included item no. 110 – 'Disable full audit trail changes False › True' and a large number of other changes all carried out on the 9th January 2014. There was no change control for the changes made and a number of the entries appeared to reduce rather than enhance the security settings (i.e. unrestricted › silent) [*It is acknowledged that the company conducted an investigation into these changes during the week of the inspection and had raised deviation number 40331 in this regard*].

Reference: EU GMP Guide, Part I, Annex 11, Principle & Paragraphs 1, 2, 4.1, 4.2, 4.7, 8.2, 9 & 10; EU GMP Guide, Part II, Paragraphs 5.40, 5.41, 5.43, 5.44, 5.47, 6.10 & 7.33

Validation

5. With respect to the process re-validation of the following was observed:-

5.1 The protocol did not provide for acetonitrile testing to be conducted on individual drums from each of the two loads for each validation batch manufactured. It was noted that the reason the validation study had been conducted was due to concerns raised regarding the homogeneity of the acetonitrile levels in the dried product, so it is considered that the validation should have extended to incorporate sampling and testing of residual levels in the individual drums;

5.2 The protocol instructions for samples to be taken from the Glatt Bowl during the validation study were not sufficiently detailed and it was considered that there was potential for ambiguity;

5.3 There was no discussion documented in the validation report regarding the which gave an atypical result in the laboratory (event 27417) for a sample taken from the Glatt following on from which it had been decided to test the individual drums from that load, which confirmed the original atypical result. In addition, the RSD for the nine drums tested was 30% which was on the limit of the acceptance criteria of ≤ 30%;

5.4 No consideration had been given to validation/re-verification of the hold times for the intermediate stages (*It is understood that the original hold times had been provided by the Customer and no new data had ever been generated by the company to verify the hold times in place*);

5.5 The routine sampling instructions in the batch record were ambiguous in that it included the following statement - 'It is best to take one sample from close to the dryer bowl wall and one from the centre of the bowl'.

Reference: EU GMP Guide, Part II, Paragraphs 12.4 & 12.5

Complaints and Recall

6. In relation to complaints the following was observed:-

6.1 Inadequate documentation was retained with customer complaint number 26121 relating to communication with the customer, including notification of the outcome of the investigation into the complaint;

6.2 The procedure entitled 'Customer Complaints' (HE.DQ.SOP.170.1.EN) did not require re-occurrence check of similar issues to be performed and documented as part of investigations performed.

Reference: EU GMP Guide, Part II, Paragraphs 15.10, 15.11 & 15.12

IV Points for Clarification

1. As discussed during the inspection, the company is requested to clarify how it considers it meets the requirements of Paragraph 4.31 of Chapter 4 of the EU GMP Guide, Part I, with respect to major pieces of analytical equipment (e.g. HPLC's, GC's).
   [*Paragraph 4.31 - Logbooks should be kept for major or critical analytical testing, production* equipment, *and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out*].
2. The company is requested to forward a copy of its report which was under compilation at the time of the inspection relating to potential for cross contamination of solvents within its tank farm, once completed. The company is requested to provide confirmation that the final report will be forwarded to the HPRA and a target timeline for completion.
3. It was observed that a number of OOS reports had been raised for elevated levels of the impurity PD151589 in stability batches of in the period since the last routine HPRA inspection in February 2013. It was understood by the inspector that this is a manufacturing impurity and not a degradation product so the company is requested to 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.

V Points to Note

1. The company was requested to review the accuracy of its Active Substance Registration (ASR) and to initiate an update as required, in consultation with the licensing section of the HPRA. It was noted that for the 'Hydrate' was specified on the ASR and the 'Hyclate' was reflected on the GMP Certificate and this was the form manufactured at the site at the time of the inspection. In addition, was specified on the ASR and the 'Hydrochloride' was reflected on the GMP Certificate and this was the form manufactured at the site at the time of the inspection.
2. For the Empower 3 System the company was requested to review its system policy which permitted the use of 'annotation tools', with respect to potential impact on data integrity.
3. It is recommended that the company introduces a policy of sampling the contents of solvent tanks following unusual events (e.g. refilling following purging, significant maintenance events).
4. An assessment should be performed by the company into the adequacy of performing single point 'in air' calibrations of the ozone meters within the B10 purified water generation plant. It is noted that the ozone meters within the B01 purified water generation plant were performed 'in water' and over numerous points.
5. It is recommended that the company introduces a section within all relevant batch processing records to record the temperature of the foil heat sealing machine, as this had been identified as a potential root cause for the failure of bag seals.

Recommendations
Not Applicable.

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:** _____
Catherine Neary
Inspector

Signature of Inspector: _____ **Date:** _____
Alfred Hunt
Inspector

Organisation: Health Products Regulatory Authority

Distribution: Hovione Limited
Health Products Regulatory Authority

Annex 1

List of personnel met during the inspection:-

Name	Title
Róisín Hickey	QA Director
Brian Walsh	Qualified Person
Anthony Breen	Qualified Person
Luisa Paulo	Corporate Compliance Senior Director
José Lisboa	Corporate QA Director
Paul Downing	General Manager
Liam O'Keeffe	Maintenance Manager
Bryan Mulcahy	QA Validation Specialist
Michael Foreman	QC Technical Specialist
Tom Davis	CSQ Specialist (QA)
Ian O' Brien	QC Technical Specialist
Ruben Pires	QC Director
Teresa Barao	Corporate Head of QA Validation
Mark Fitzgerald	Warehouse Supervisor
Tracey O'Callaghan	B10 Process Engineer
Jorge Falcão	B10 Production Manager
Alex Matos	B10 Production Team Lead
Marco Marques	Manufacturing Director
Robby Dupuy	Production manager B01
Stephen Galvin	Engineer
Clare Mc Elroy	B01 process Engineer
John Sisk	B01 Supervisor
Noel Walsh	B01 Operator
Ger Moore	B01 Operator
João Rino	Business Application Responsible (Corporate)
Emma Mc Gibney	QA Specialist
Sarah Downing	QA Specialist
Paolo Croce	QA Specialist
Anna O' Dowd	QA Specialist
Carmel Pyne	Technical Services Director
Mike O'Sullivan	Technical Services Chemist
Sarah Breen	QC Team Lead
Claire Walsh	QC Team Lead
Paulina Radaczynska	Supply Chain Specialist
Maurice Cleary	Safety Engineer