DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH

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Division International Drug Quality
International Compliance Branch
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December 17, 2014

James Harvey
General Manager
Hovione Limited
Loughbeg
Ringaskiddy, Co. Cork
Ireland

Reference: FEI 3008058822

Dear Mr. Harvey:

We have completed our review of the Establishment Inspection Report (EIR) for the inspection conducted at your Active Pharmaceutical Ingredient (API) and intermediate manufacturing facility in Ringaskiddy, County Cork, Ireland by Investigator Brittany Terhar during the period of July 21, 2014 to July 25, 2014.

Based on the profile class covered during the inspection, we are classifying your facility as acceptable. This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to assure continued compliance with current good manufacturing practices (CGMPs).

Please be advised that all manufacturers must register annually as required by 21 C.F.R. § 207.40. Information on how to register is available at http://www.fda.gov/cder/drls/registration_listing.htm.

Additionally, we enclose a copy of the establishment inspection report (EIR). Releasing this EIR to you is part of FDA's effort to make its regulatory process and activities more transparent to the regulated industry. It is being provided to you for information purposes only and may reflect some redactions made by the Agency in accordance with the Freedom of Information Act and 21 C.F.R. Part 20. Copies provided to other requestors may have additional redactions of trade secret and confidential commercial information.

If you have any questions regarding this letter, you may contact me at the above address or number.

Sincerely,

Maan Abduldayem
Branch Chief (Acting)
Division of International Drug Quality

Enclosure: EIR

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SUMMARY

This product specific and GMP inspection of an active pharmaceutical ingredient and intermediate manufacturer was conducted per FACTS Assignment ID 9284754 and Operation ID 7278783. This inspection was conducted at the request of the CDER International Compliance Branch and Division of Foreign Field Investigations (Trip No. 2014-229D).

This inspection was conducted in accordance with CP 7346.832 Pre-Approval Inspections and 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection. The inspection included

review of the Quality System, Production System, Facilities & Equipment System, Materials System, and Laboratory System.

The previous inspection, conducted 03/12-03/16/2012, resulted in the issuance of a four item FDA 483, Inspectional Observations. The items were:

- Failure to follow procedure entitled "Stability" HQ.CCO.COP024.4.EN
- Deviations are not closed in a timely manner.
- Required environmental monitoring did not occur on the first day of filling/packaging for [redacted]HE00003.
- Monthly calibration for the MX5 Microanalytical Balance used out of date calibration weights.

The current inspection revealed the firm continues to operate as an active pharmaceutical ingredient and intermediate manufacturer. Inspection coverage included review of the profile class CSN, Non-sterile API by Chemical Synthesis, and CRU, Non-sterile Intermediate, with specific coverage of the intermediate [redacted]. [redacted] is the applicant for [redacted] for [redacted] Tablets of which [redacted] Spray Dried Dispersion is an intermediate. The firm was not manufacturing any product during the inspection due to a full recalibration of the site.

At the conclusion of the inspection, no FDA-483 was issued. I informed management, the final decision determining the compliance of a firm is at the discretion of the Center for Drug Evaluation and Research (CDER), Office of Compliance, after review of the written report. I did not encounter any refusals during this inspection and no samples were collected. The firm's drug registration is current. Corrections from the previous inspection were verified.

ADMINISTRATIVE DATA

Inspected firm:	Hovione Limited
Location:	Loughbeg Ringaskiddy, Co. Cork, Ireland
Phone:	353 21 451 2856
FAX:	353 21 437 8697
Mailing address:	Loughbeg Ringaskiddy, Co. Cork, Ireland
Dates of inspection:	7/21/2014, 7/22/2014, 7/23/2014, 7/24/2014, 7/25/2014
Days in the facility:	5

Participants: Brittany D. Terhar, Investigator

Upon arrival to Hovione Limited located at Loughbeg, Ringaskiddy, Co. Cork, Ireland, I introduced myself and exchanged business cards with the individuals present. Mr. James Harvey, General Manager, identified himself as the most responsible individual on site.

I am the sole author of the establishment inspection report.

HISTORY

This firm is a contract manufacturer manufacturing active pharmaceutical ingredients and intermediates. The firm's products consist of 58% generics, 27% exclusives, 12% particle design and 3% pharma. This site was acquired from Pfizer in April of 2009. The firm has other manufacturing locations in New Jersey, USA, Loures, Portugal, Taizhou, China and Macau, China. The firm's corporate headquarters is located in Loures, Portugal.

The firm has 144 full-time employees which includes 20 full-time contract employees and 1 part-time employee in the engineering department. The firm's office hours are 9:00a – 5:30p, Monday – Friday. The firm's manufacturing and laboratory runs 24/7 on two 12 hour shifts, 7:30a – 7:30p and 7:30p – 7:30a. The firm's drug registration is current.

The last inspection of the firm was conducted on 03/12-03/16/2012. The inspection covered the Quality, Production, Materials, Facilities & Equipment and Laboratory systems with specific coverage of profile class CSN and the product [redacted] The inspection resulted in the issuance of a four item FDA 483, Inspectional Observations. The items were:

1. Failure to follow procedure entitled "Stability" HQ.CCO.COP024.4.EN
2. Deviations are not closed in a timely manner.
3. Required environmental monitoring did not occur on the first day of filling/packaging for [redacted]HE00003.
4. Monthly calibration for the MX5 Microanalytical Balance used out of date calibration weights.

Regulatory and U.S. Agent
Ms. Dirce Macario
Hovione LLC
40 Lake Drive
East Windsor, NJ 08520
dmacario@hovione.com
Phone: 609-918-2600 or 866-918-2601
Fax: 609-918-2615

FMD-145 AND OTHER POST-INSPECTIONAL CORRESPONDENCE

Please send the FMD-145 letter to:

James Harvey, General Manager
Hovione Limited
Loughbeg
Ringaskiddy, Co. Cork
Ireland
jharvey@hovione.com

Please send all other post-inspectional correspondence to:

Guy Villax, CEO
Hovione FarmaCiencia SA
Sete Casas
2674-506 Loures
Portugal

INTERSTATE COMMERCE/ JURISDICTION

The firm currently manufactures two products for the U.S. market, [redacted] and [redacted] has a Hovione code of 17LY01 and [redacted] has a Hovione code of 17BB01. Please see **Exhibit 1** for a list of [redacted] batches manufactured since the last inspection. Of the [redacted] batches manufactured only two were shipped to the U.S. These batches are marked US on **Exhibit 1**. Mr. James Harvey, General Manager, stated on 07/25/2014, the firm does not intend to manufacture [redacted] anymore. Please see **Exhibit 2** for a list of [redacted] batches manufactured since the last inspection. The last batch of [redacted] shipped to the U.S. was on 08/31/2012. For a list of all shipments to the U.S. see batches highlighted in yellow on **Exhibit 2**. The firm stated for the [redacted] product they have no way of knowing if the product is going to be shipped to the U.S. or not when manufacturing. However, currently all [redacted] product is being shipped to Europe.

[redacted] Spray Dried Dispersion (SDD) batches, referred to at this site as WG06, shipped to the U.S. are listed in the attached **Exhibit 3**. These batches consist of one development batch and two validation batches.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Please see **Exhibit 4** for current organizational charts.

James Harvey, *General Manager*, is the most responsible individual located on site. He was present for the opening discussion, discussion regarding the recalibration of the site and the closing discussion. Mr. Harvey reports to Luis Gomes, VP of Manufacturing.

Roisin Hickey, *Director of Quality Assurance*, is responsible for everything related to Quality Assurance and Compliance. This includes managing the department, review and approval of documentation (validation documents, change control, complaints, etc.). She communicates with regulatory agencies, participates in risk assessments, audits/inspections and is the lead internal auditor for the site. Ms. Hickey has been in her current position and with the firm since 09/02/2013. She reports to Jose Lisboa, Quality Assurance Director, located at the Portugal site. Ms. Hickey was present for all portions of the inspection and provided information present within this report.

Sarah Scott, *Quality Assurance Specialist*, is the QA support for the [redacted] Spray Dried Dispersion product. Ms. Scott has been with Hovione since November 2010 and has been with the firm since April 2010. Ms. Scott was present for a majority of the inspection including the opening and closing discussions. She provided information present within this report. Ms. Scott reports to Ms. Hickey.

Joana Reymao, *Compliance Manager*, has responsibility for adopting policies on site, training, is a part of the internal audit program and reviews and approves SOPs. She has been with Hovione for 8 years and has been in her current position since May 2011. Ms. Reymao was present for a majority of the inspection including the opening and closing discussions. She provided information present within this report. Ms. Reymao reports to Ms. Hickey.

Luisa Paulo, *Director of Compliance*, is part of the corporate audit team and her main function is to make sure quality is in place at all sites. She has been in her current position since 2004 and has been with Hovione for 31 years. Ms. Paulo reports to Guy Villax, CEO. She was present for a majority of the inspection including the opening and closing discussions.

Additional personnel with whom I had contact and discussions with during the inspection includes but is not limited to: Anthony Breen, Senior QA Specialist, Brian Walsh, Senior QA Specialist, Jose Lisboa, Corp. QA Director, Eric Flynn, Director of Engineering, Marco Marques, Director of Manufacturing, Ruben Pires, Quality Control Director, Liam O'Keefe, Maintenance Manager, Tracy O'Callaghan, Process Engineer B10.

FIRM'S TRAINING PROGRAM

I reviewed the firm's training procedure, HQ.CCO.COP007.4.EP. Each job function has a competencies matrix listing all of the required competencies for that specific job. A specific competency may include training courses and training sessions followed by an evaluation of the

individuals understanding. Evaluations may include etests, paper tests, or practical demonstration. An individual training plan will take into account the job competence matrix and previous experiences. New employees must complete their training in 12 months. However, there are portions of the training which require completion within 90 days such as the Health and Safety portion. Job matrixes and individual training plans are re-evaluated every year. Main training modules must be completed every three years, this includes GMP training. However, procedural updates could prompt training. The firm uses the program Trainstream to log their training.

I reviewed the individual training plan and completions for Tracy O'Callaghan, Process Engineer B10.

QUALITY SYSTEM

I reviewed the firm's 17BB01 FY2013 Product Quality Review (PQR), HE.QSR.AR139.1.EN, which is the annual review for [redacted] The review went over batches manufactured, batch deviations, complaints, production performance (yields), analytical test results, out of specification results, manufacturing/process changes, analytical methods/specification changes, stability, returns, recalls, validation and qualification status. I did not note any issues with the PQR.

Please see section titled **Complaints** for more information regarding the complaint process. Please see section titled **Recall Procedures** for more information regarding recalls.

The firm provided me with a list of deviations, including both process deviations and laboratory out of specifications, for [redacted] SDD (19WG06-[redacted]. From the list of 57deviations, I randomly selected 13 deviation records to review. I was provided with a similar list for [redacted] (BB01) and [redacted] (LY01). I selected and reviewed 3 deviation records for both [redacted] All investigation reports and associated CAPAs appeared adequate. I reviewed the firm's procedure, Deviation Records, HQ.CCO.COP014.10.EP. The procedure states on **(Exhibit 5) page 5**, "A deviation record should be raised within two working-days from the time the deviation is detected". Throughout the review of the deviation records I found the date of detection was not a required element of the record and also that this requirement was not always being followed. Specifically there were two instances out the 19 deviation records reviewed that were not created within the two day time frame. Please see **General Discussion with Management** for more information. During my review of the deviation records I also found that due to the need for customer approval or review of records, deviations were not always closed out within the 45 day timeframe allowed by the deviation procedure. In these cases, the deviation records had an approval of a closure date extension either within the deviation report or attached to the deviation report. The extension documentation was not always promptly added to the report. At times there were gaps in the due date and the date

the extension documentation was added. Please see **General Discussion with Management** for more information.

I reviewed the following procedures: Reprocessing, reworking and returned products, HQ.CCO.COP028.1.EN; Reprocessing and Reworking of Products, HQ.DQ.SOP002.10.EN; and Returned Products, HE.DQ.SOP165.0.EN. According to the firm's reprocessing procedures, a product can only be subject to 3 consecutive processes of reprocessing/reworking. The reprocessing/reworking procedure does not discuss specific instances when reprocessing/reworking is allowed. I reviewed the reprocessing of two batches of [redacted] Spray Dried Dispersion. Please see the **Production System** for more information. Returns are separated into different categories. A return is designated as an "A" return if the quality of the product is in question. A return is designated as a "B1" return if the packaging is not opened and the quality of the product is determined to be intact. A return is designated as "B2" if the packaging is opened or damaged. A and B2 returns are labeled as "Returned" and should be resampled. Please see **Exhibit 6** for Returned Products flowchart.

I was provided a list of rejected finished product and rejected raw materials. I reviewed all rejected finished product batches listed (7 batches) and 4 out of the 7 listed batches of raw material. The reason for rejection and any additional investigation was reviewed. During review of rejected material, I found the firm's system requires them to put batches into rejected status in order to reprocess them. Specifically for [redacted]SDD, lots 19WG06-[redacted]HE00004 and 19WG06-[redacted]HE00007, the firm put these batches into rejected status so they could reprocess them. The batches were rejected for no other reason than to conduct a reprocessing and scale-up study. These batches met specifications, thus there was not a deviation and a reason for rejection was not documented. There is a protocol for this study; however, the protocol does not list batch numbers. At the time of the protocol creation the batch numbers were unknown. The same situation occurs when a raw material is rejected due to reaching is expiry date or if the material is no longer needed. A deviation has not occurred so documentation in a deviation report is not done. The firm was able to explain in every instance why specific batches were rejected, but detailed documentation was not available in SAP or written records. I discussed this with the firm. Please see **General Discussion with Management** for more information.

The firm uses an electronic quarantine system. Please see the **Materials System** for more information. Please see **Firm's Training Program** for more information regarding training.

Change Management Program

I reviewed the firm's procedure, Change Control, HQ.CCO.COP027.6.EN. The procedure discusses types of changes, individual responsibilities, and the procedure. The process consists of a pre-assessment of the proposed change and a six-phase change request process. The phases include: Phase 1 – Description of the current system with justification of the proposed change, Phase 2 – Impact assessment of the change, Phase 3 – Implementation plan proposal, Phase 4 –

Approval of the change proposal, Phase 5 – Evaluation after implementation, and Phase 6 – Closure. Hovione's change control document is referred to as a PdA. PdAs are issued electronically through a change control information system. Paper PdAs may be used as a contingency plan.

I was provided with a list of changes for the following products: [redacted], [redacted] and [redacted] SDD. I selected and reviewed PdA 6455, 6274, and 5999 related to [redacted] SDD, PdA 5123 related to [redacted] and PdA 5749 and 5720 related to [redacted]. The firm appeared to be following their procedures and evaluating the change as necessary.

MATERIALS SYSTEM

On 07/21/2014, I visited the firm's main chemical warehouse, B23. This is where raw materials and finished products are stored. The firm does not store any product on wooden pallets. If wooden pallets are used to transport the product, the product is immediately transferred to plastic pallets upon receipt. When the firm receives a raw material they fill out a Packaging/Chemical Product Reception form. After completion the raw material will be booked into inventory in SAP and will go into Quality Inspection status. Every container of raw material receives its own unique label with barcode. When this is complete the material is ready to be put away into racks or ready for sampling. The standard rule the firm uses for sampling containers is $\sqrt{n}+1$. The firm tests all raw ingredients for identity. The number of containers tested is the same as the standard rule listed above, where n is the total number of containers in the batch. The firm's procedure, HE Sampling Procedure, HE.DQ.SOP151.7.EN, discusses sampling procedures, labeling of samples and containers to use for samples. If full testing of the ingredient is required a composite sample from all containers sampled is used.

Quarantine of material is controlled using SAP. However, if a material is rejected it is also moved to the reject cage within the warehouse. The status of material in SAP can be Quality Inspection status which either requires sampling or approval by the quality department, Restricted Use, which is generally used for rejected material, Blocked status which is used when an investigation is ongoing, Reserved for when a material has been allocated for a future requirement and Unrestricted Use when the material is approved and available for use.

I reviewed the firm's supplier qualification process and reviewed their procedure, Supplier Qualification, HQ.CO.SOP105.3.EN. The firm's supplier qualification process is risk assessment driven and is composed of four phases – selection, approval, qualification and monitoring. The risk is calculated using the procedure set forth in the SOP, Risk Assessment, HQ.CO.SOP105-A1.2.EN (**Exhibit 7**). The firm's procedure requires them to know the full supply chain for high risk materials. The full supply chain includes all locations where material is manufactured, propagated, processed and handled before it is supplied to Hovione. The firm's procedure, Suppliers Monitoring and Evaluation, HQ.CO.SOP105-A4.0.EN, (**Exhibit 8**) was also reviewed

during this inspection. The procedure states, "Raw materials classified as Level 1 and 2 (reduced testing schemes) should be subjected to a full analysis on, at least one batch, at appropriate periods of time. This should be defined on a case by case and the analysis compared to the Certificate of Analysis." During the inspection, I verified the firm tested the identity of the [redacted] lot HE00018 (supplier lot [redacted], used in the manufacturing of [redacted] SDD. I reviewed the certificate of analysis. I discussed with management the full analysis of at least one batch at appropriate periods of time. Ms. Paulo stated for this specific API they will not be conducting a full analysis periodically. The supplier of the API for this product is [redacted]. The applicant for [redacted] and Hovione's customer for [redacted] SDD is [redacted], signed a Statement on Qualification of New Sources stating they request Hovione to use [redacted] as the supplier for [redacted] API and that [redacted] will be responsible for the Supplier Qualification process. Please see **Exhibit 9** for Statement on Qualification of New Sources and **General Discussion with Management** for more information.

FACILITIES AND EQUIPMENT SYSTEM

Please see **Exhibit 10,** page 1, for an aerial view of the site and page 2 for a diagram of the site.

All pieces of equipment in the [redacted] SDD process train were previously owned by Pfizer and qualified by them. The [redacted] SDD process is carried out in Building B10. B10 is a 5000 m^2 cGMP facility. I reviewed the firm's Qualification Status Assessment/Plan B10 Systems, HE.QSP.EQ260.0.EN, approved 10/25/2013. I also reviewed the associated report, Qualification Report B10 Systems, HE.QSR.EQ302.0.EN, approved 12/04/2013. I reviewed the operational qualification of the B10 spray dryer, DR-10-07-1000, in depth and verified the spray dryer could reach and maintain the required parameters.

I reviewed the firm's cleaning validation documentation for [redacted] SDD (19WG06-[redacted]. I reviewed 19WG06-[redacted] Cleaning Validation Protocol, HE.CLN.CVPL058.2.EN, approved 07/17/2014, and 19WG06-[redacted] Cleaning Validation Report, HE.CLN.CVRP027.1.EN. The firm's cleaning for the [redacted] SDD process train is divided into gross decontamination followed by cleaning. Gross decontamination is a flush with specified liquids depending on the piece of equipment. Cleaning is the strip down, manual clean, visual inspection and reassemble of the equipment. After reassemble an additional flush is conducted. Currently the firm believes the WG06 product is the worst case product manufactured in B10 and is why it is being used to validate the cleaning of the B10 equipment. The firm uses the Maximum Allowable Carry Over (MACO) to determine a pass or fail result for contaminant carryover. The MACO calculation uses the next known minimum batch size and a limit of 10 ppm of product carryover. The swab locations selected for equipment are determined by a process engineer and an experienced operator based on locations where they have seen accumulation of product in the past. I reviewed the swab locations for the spray dryer. The firm has conducted two successful cleanings following 19WG06-[redacted] campaigns. However, the second cleaning procedure was not identical to the first in that the flushes for a few

pieces of equipment were different volumes. Due to the difference, the firm will be executing an additional two cleanings. They anticipate finishing the cleaning validation documentation after the second WG06 campaign scheduled to begin in December.

The firm was not producing any products during my inspection. This was due to a complete recalibration of the site. The firm identified an issue with calibration certificates on 06/25/2014. The firm had up to date calibration certificates for pieces of equipment that were removed from the site around 2004. The instruments were still in the firm's SAP system with maintenance history from 2009-2013 and hard copy certificates from 2012. This issue was identified when as part of an equipment qualification a review of instruments calibration status was verified with Process & Instrument Drawings. It was found that safety critical instruments did not exist on the P&IDs. Physical checks in the plant also confirmed these instruments did not exist and were removed from the site before it was purchased by Hovione. On 06/26/2014, it was confirmed that at least 3 instruments had false certificates. On the same day production and product shipments were stopped. The firm's calibrations are conducted by an outside contractor. The firm has one main calibration technician and others help as needed. These process calibration technicians are present onsite at all times.

On 06/26/2014, Hovione interviewed the main calibration technician and he could not explain the existence of the calibration certificates for these instruments. On 06/27/2014, Hovione met with the contractor's management and they together interviewed the main calibration technician again. The technician admitted to falsifying calibration records for the missing instruments but claimed other instruments were being calibrated. This technician was removed from the site and his site access was disabled. On 06/30/2014, an additional 3 calibration technicians were interviewed by Hovione. One of the technicians admitted to falsifying calibration certificates. On the same day all of the contract calibration technicians from this contractor were asked to leave and their access to the site was removed. From here the firm decided to do a full site recalibration. The firm identified a new calibration company which is the same company used by the Hovione Portugal site. The new technicians were flown in on 07/04/2014 and began recalibrating instruments beginning with process critical instruments in Building 10 and [redacted] equipment in Building 1 to assess their calibration status. Please see **Exhibit 11** for the Summary of Calibration Findings provided to me by the firm. Those instruments found to be in calibration are considered to be okay by the firm using the logic that if an instrument after going through calibration shows no deviations that measuring instrument has operated within its allowable ranges. Please see **Exhibit 12** for Engineering Dept. Memorandum 14-ENG-007, dated 07/09/2014, discussing this logic. The firm also used Delta V trends, data trends, in order to determine if calibrations were conducted. I went through current calibration data for critical instruments for the [redacted] process and B10 equipment. I did not note any issues. The firm has implemented many CAPAs in response to this incident. These include updating contractor training, qualifying a new calibration contractor, recalibrating all site instruments, blocking access to old calibration technicians, checking all instruments in SAP against the field and P&ID and instituting the attachment of Delta V trends to calibration records when available. Please see **Exhibit 13** for an example of a temperature transmitter calibration and the attached Delta V trend.

The firm's analytical instruments are not affected by this incident as they are managed by a separate company, primary data must be attached to the calibrations, and someone is present with the calibration staff in the laboratory while they perform calibrations.

PRODUCTION SYSTEM

On 07/21/2014, I did a walkthrough of Building 10. Building 10 is where [redacted] Spray Dried Dispersion is manufactured. I walked through each piece of equipment in the [redacted] SDD process. The firm was not manufacturing any product during the entire inspection. Please see **Exhibit 14** for [redacted] SDD (19WG06-[redacted]) Process Flow Diagram. The main steps of the process include feed solution preparation, spray drying, secondary drying and bulk packaging. On 07/21/2014 I also conducted a walkthrough of Building 1. Building 1 is where the APIs [redacted] and [redacted] are manufactured. The firm was not conducting any manufacturing in Building 1 during the inspection.

I reviewed the firm's most recent Master Batch Record, HE.PRD.BPR.19WG06-[redacted]03.0.EN, for [redacted] Spray Dried Dispersion. The master batch record has been updated for a new batch size of 546 kg. According to management, 546 kg is the largest batch size planned for this product. I also reviewed the changes that have been made to the batch record since the last batch was produced.

I reviewed the firm's scale up campaign for [redacted] SDD which included 4 batches of 350 kg of starting total solids. The batches in the campaign included 19WG06-[redacted].HE00003, 19WG06-[redacted].HE00004, 19WG06-[redacted]HE00007, 19WG06-[redacted].HE00009, and 19WG06[redacted].HE00009.02. Lot 19WG06-[redacted]HE00003 was a scale up Development B batch. Lot 19WG06-[redacted].HE00004 was referred to in the scale up protocol as Lot A and was also manufactured as a scale up Development B batch. Lot 19WG06-[redacted]HE00007 (referred to as Lot B in the protocol) resulted from the reprocessing of lot A. Lot 19WG06-[redacted].HE00009 (referred to as Lot C in the protocol) resulted from the reprocessing of lot B. 19WG06-[redacted]HE00009 was split into two loads after the spray dry process. Load 1 of 19WG06-[redacted]HE00009 followed normal process and went directly to secondary drying. Load 2 was renamed as Lot 19WG06-[redacted].HE00009.02 and was held in an intermediate bin container (IBC) for 7 days to study the effect of a wet hold. After 7 days the material was dried in the secondary drier. The protocol, 19WG06-[redacted] Scale Up Campaign Protocol, HE.QSP.PV008.0.EN, and report, 19WG06-[redacted] Scale Up Campaign Report HE.QSR.PV172.0.EN, for this campaign were reviewed. I also reviewed the Summary of Results, HE.QSR.PV172-A1.0.EN, for the campaign described above. I did not note any issues. I reviewed the available stability results for lots 19WG06-[redacted]HE00009 and 19WG06-[redacted]HE00009.02. See Laboratory Control System for more information.

I reviewed the firm's Validation Master Plan for [redacted] Spray Dried Dispersion, 19WG06-[redacted] Validation Master Plan HE.QSP.VMP058.0.EN. I also reviewed the Process Validation Protocol 19WG06-[redacted] HE.QSP.PVP145.1.EN, for 350 kg starting solids batch size. I reviewed the associated report, 19WG06-[redacted] Process Validation Report, HE.QSR.PV176.1.EN and Homogeneity Results: HE.QSR.PV176-A1.0.EN. The batches involved in this campaign included: 19WG06-[redacted]HE00021 –

HE00023. HE00021 was manufactured using API from [redacted]. HE00022 was manufactured using a mixture of API from [redacted] and [redacted]. HE00023 was manufactured using API from [redacted] There were 20 deviations raised in relation to the validation campaign (3 batches). Of the 20 deviations 7 were process related and 13 were Q.C. finished product testing/homogeneity testing related. One of the deviations was classified as a critical deviation, deviation no. 31351. I reviewed this deviation and had no issues with the investigation or the corrective/preventive actions taken. Please see **Exhibit 15** for 19WG06-[redacted] Process Validation Report – Deviations, HE.QSR.PV176.A2.0.EN.

The firm will be conducting an additional 3 batch process validation campaign under, Process Validation Protocol, HE.QSP.PVP172.0.EN for the validation of the 546 kg batch size. This has not been conducted to date.

LABORATORY CONTROL SYSTEM

On 07/21/2014, I did a walkthrough of the firm's Quality Control Laboratory. The laboratory is located in in the building referred to as the Technical Building. The laboratory conducts assay and degradant HPLC testing, GC residual solvents testing, IR and also conducts some wet chemistry. The laboratory has 16 HPLC units and 9 GC units.

During the walkthrough I spot checked a reference standard to make sure it was within expiry and verified a certificate of analysis was available.

Sample numbers are created by the LIMS system and are sequential. Docstream is the system where test methods are maintained. Analytical data is maintained in a notebook and then the information is transcribed in the LIMS system. The data is then reviewed in LIMS as well as in the notebook.

During the inspection, I verified the analytical methods submitted with the application for [redacted] Spray Dried Dispersion [redacted]) are the same as those analytical methods being used at this site. I reviewed the firm's method validation for 19WG06-[redacted]: Identification, Assay and Related Substances. The method validation at the Loures site and transfer from the Hovione Loures, Portugal site to this site were done concurrently. The firm also conducted a supplemental study for accuracy. This information was added to the original report and a new report was created. Please see **Exhibit 16** for CRLC4302-FP1: 19WG06-[redacted] Identification, Assay and Related Substances (by HPLC) – Validation Protocol, HQ.QSP.MV572.0.EN. Please see **Exhibit 17** for 19WG06-[redacted] CRLC4302: 19WG06-[redacted] Identification, Assay and Related Substances (by HPLC) – Accuracy Supplemental Protocol, HQ.QSP.MV572-A2.0.EN. Please see **Exhibit 18** for CRLC4302: 19WG06-[redacted] Identification, Assay and Related Substances (by HPLC) – Validation Report, HQ.QSR.MV1046.1.EN. The parts of the validation performed by this site included Formal Transfer Type II/ Reproducibility, Formal Transfer Type II/ Inter laboratory Study, and Formal Transfer Type

II/ LOD and LOQ. All testing passed their predetermined acceptance criteria. I did not note and issues.

Please see **Exhibit 19** for a list of all testing conducted on [redacted]SDD, associated analytical method and whether the testing is done at HE (Core, Ireland) or SC (Loures, Portugal).

Please see **Exhibit 20** for a list of batches on stability and the associated stability protocol. All stability testing with the exception of timepoint zero is conducted at Hovione located in Loures, Portugal.

I reviewed the most recent results obtained for stability testing of [redacted]SDD lots 19WG06-[redacted]HE00009 and 19WG06-[redacted]HE00009.02 from time zero to 6 months for all conditions. The testing appeared to be conducted at time points consistent with the protocol and all results were within specification. Please see **Exhibit 21** for the protocol, 19WG06-[redacted]Bulk Powder – Stability Protocol, HE.SSD.SP151.4.EN. I reviewed the firm's newest stability protocol for [redacted] SDD, HE.SDD.SP254. The only difference to the new protocol from HE.SDD.SP151 is the long term testing condition of 30±2°C and 75±5% RH. I reviewed the summary of results for lot 19WG06-[redacted]HE00023 to date. The results were all within specification and appeared to be collected according to the protocol. Additionally I reviewed the stability results for lot 19WG06-[redacted]HE00001 from time point 0-12 months. I reviewed the raw data associated with the assay result obtained from the 12 month time point at conditions of 25±2°C and 60±5% RH. I also reviewed the raw data associated with the related substances results obtained from the 6 month time point at conditions of 40±2°C and 75±5% RH. I did not note any issues. The firm uses Empower software for their chromatograms and area data. The information from Empower is then transcribed into LIMS which does the calculations. This software is also used at the corporate location where stability testing is conducted. This is how I was able to review the raw data for stability conducted at Loures, Portugal. I did not review the laboratory notebooks related to the stability results.

I reviewed the raw data associated with the finished product release results obtained for [redacted] lot 19WG06-[redacted]HE00025. Specifically I reviewed the raw data associated with related substances, assay and residual solvents. I verified the raw data entered into LIMS, reviewed the data in Empower and reviewed laboratory notebooks associated with these results.

Characterization by XRPD is a release test and stability test for [redacted]Spray Dried Dispersion. This testing is conducted at Hovione located in Loures, Portugal. During the inspection, I obtained HQ.AA.RX4066: 19WG06-[redacted] Characterization by X-Ray Powder Diffraction (XRPD) – validation report, HQ.QSR.MV1018.0.EN (**Exhibit 22**). The validation assessed the following analytical parameters: Selectivity, Repeatability, Robustness, and Intermediate Precision. This is consistent with the firm's procedures.

MANUFACTURING CODES

The firm's manufacturing codes are a combination of alphabetical and numerical characters.

Example: 19WG06-[redacted]HE00001
19 = drug intermediate product
Others: 17= API exclusive, 16 = API intermediate exclusive, 05 = API generic, 04 = API intermediate generic
WG = [redacted] (two letters assigned to client)
06 = 6th product (number sequential for products for specific client)
[redacted]
HE = Cork, Ireland manufacturing site (HQ = Loures, Portugal manufacturing site)
00001 = sequential number

COMPLAINTS

I reviewed the firm's complaint procedure, HQ.CCO.COP029.6.EN, Handling of Complaints. The procedure discusses the information that must be present in the complaint log. The firm has had one complaint since the last inspection. I reviewed the complaint and the complaint investigation. The complaint was associated with the API [redacted] Lot 17BB01.HE00142. The complaint was received from [redacted] who had found plastic and wood particles during the sieving process of a blend which contained several materials, one of which was [redacted] The investigation went through each step in the [redacted] process and ruled out packaging materials, environment, people, measurement, methods and equipment as potential causes. The foreign material was analyzed and was 75% plastic. The particles were sent to Hovione for visual examination and the material did not appear to be consistent with materials used at Hovione. The firm ruled out Hovione as the source of the foreign material. The investigation appeared appropriate and the procedure was followed.

RECALL PROCEDURES

I reviewed the firm's procedures HQ.CCO.COP030.1.EN, Product Recall, and HE.DQ.SOP149.4.EN. Recall SOP. Both procedures appeared adequate. The firm conducts a mock recall every year. The last mock recall was conducted in March of 2013. The firm stated they have not been involved in any recalls since the last inspection.

REFUSALS

I did not encounter any refusals during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

The close out meeting was held at Hovione Limited on July 25, 2014. A full list of individuals present during the discussion with me is attached as **Exhibit 23.**

During the close-out meeting with management I discussed what was covered during the inspection and the inspection should not be considered all inclusive. I also discussed the below items with management:

1. If product is rejected for no other reason than to reprocess the batch, or if a material is rejected due to reaching its' expiry or just no longer needed, the reason for rejection is not clearly documented.

   The firm's procedure Quality Control of Products, HQ.CCO.COP017.5.EN, was updated in order to more clearly state the requirement for a reason for rejection. The updated procedure was reviewed. A new Internal Operating Procedure for the warehouse, Destruction of Materials, HE.WH.IOP022.1.EN, was also created. I reviewed this new procedure.
2. The firm's procedure for deviations states time from detection to creation of deviation should be within two days. However, the firm's deviation documentation does not have a field for detection date nor does it require this to be entered into a different field. The date of occurrence is clearly designated but this is not always the date the deviation was detected.

   Management stated the form will be updated to include the detection date as a required field. The appropriate procedure will be updated as well.
3. Justification documentation provided for the extension of deviation closure timeframes is not always prompt.

   I discussed this with management due to the closure of deviations being an issue during the last FDA inspection.
4. Full testing of raw materials annually, as required by their procedures, is not conducted when the customer is responsible for the Supplier Qualification process as stated in writing.

   I discussed with the firm the written documentation does not clearly state the supplier is responsible for verifying the suppliers COA at appropriate intervals. Management stated they would discuss this with their customer.

I informed management the final classification on the firm's compliance will be made by the Office of Compliance after review of the establishment inspection report.

ADDITIONAL INFORMATION

Follow-up to CDER Questions

Below is a follow-up to questions provided by CDER in the attached document, Inspectional Assignment (Email Transmittal) dated July 18, 2014.

III. Manufacturing

a. Solution Preparation

i. I reviewed the firm's 19WG06-[redacted]: Feed Solution Stability Protocol, HQ.SSD.171.1.EN. This study was conducted in Portugal. The study was conducted by placing equal amounts of feed solution in two reactors at 25°C. Two samples one from each reactor were taken at time point zero. After two hours one reactor was increased to a temperature of 30°C. Both reactors were set under an inert atmosphere at constant 1.1 bar gas pressure and with an agitation speed of 75 RPM. Samples of 5 mL were taken at time 0, 24 hrs, 48hrs, 7 days, 14 days, 21 days, 24 days, 28 days and 31 days. The samples were tested for assay and related substances. Instructions for the charging amounts of solids and [redacted] are present within the batch record. The approved hold times are not included in the batch record. All process parameters are present within the batch record as well.

ii. The firm's [redacted] solution preparation process is based on the free base active ingredient amount (using the drug content factor) not on the total kilogram amount. During the inspection, I had the firm conduct a back calculation from the amount of [redacted] and solids put into lot 19WG06-[redacted]HE00022. I verified [redacted] was accurate.

b. Spray Drying

iii. The parameters of the spray dryer are record at the beginning and the end and at least every 30 minutes in between. If the process parameters were to fall out of the range the operator would switch over to solvent only to allow the system to stabilize. After the system has stabilized the operator would switch back to product. If something was showing to be really wrong then they would shut the system down and investigate. This information is not present within the batch record. However, I was told the operators would know to switch over to solvent. Please see the Quality System for information regarding investigations, deviations, CAPAs and change control.

iv. The firm conducted a tech transfer campaign in April of 2013. The tech transfer was conducted in three different stages. Stage 1 was to conduct 1 GMP batch of [redacted] SDD with [redacted] of starting solids aiming at a [redacted] Stage 2 was to conduct 5 trials for identifying the best process conditions to product wet spray dried dispersion with target properties based on development work carried out at the Loures, Portugal site, bulk density of [redacted] and particle site (D50) of [redacted] Stage 3 was to conduct 9 spray drying trials structured in a central composite face-centered DOE to support normal operating ranges. I reviewed the report for this study, WG06 – April 2013 tech transfer campaign (HE).

v. The firm has conducted the reprocessing of this material twice. However, the material was of acceptable quality when the reprocessing was conducted. It was conducted as a study. Please see the Production System for more information. Hovione stated at this time for commercial [redacted] SDD they do not intend on conducting any reprocessing. Thus, the firm has not established any limits or procedures specific to [redacted] SDD.

vi. Please see III. b. iv. above.

IV Quality Control / Quality Assurance

a. Quality System

i. See Quality System section above.

b. Finished Product Testing

i. Please see Laboratory Control System above. Hovione located in Loures, Portugal conducts the X-ray diffraction testing for this location. Communications made with the Loures site indicate a qualitative validation was completed for XRPD testing, not quantitative. Management stated data was submitted to the center showing quantitative validation for this test does not need to be conducted.

ii. Sampling procedures used for finished products are the same as those used for raw materials.

c. Validation
i. See Production System.
ii. See Facilities and Equipment System.
e. Stability

i. The stability data found in the application was related to a batch manufactured at the Loures, Portugal site. I reviewed stability data and raw test data. Stability samples are stored at Loures, Portugal and all testing with the exception of time point zero are conducted there. Please see Laboratory Control System for more information.

d. Raw Materials
i. See Quality System.
ii. See Materials System. The API, [redacted] was selected for review.

e. Distribution Supply Chain:
i. The firm's procedure requires them to know the identity of the whole supply chain to the manufacturer for critical materials. Please see Materials System.

Logistics and Accommodations

I stayed at the Maryborough Hotel and Spa. The hotel is approximately 20 minutes by car to the plant. The hotel was comfortable and within walking distance to restaurants. The hotel rate per night increased on the weekends and thus was over per diem on the weekends. The firm provided daily transportation to and from the plant and also provided transportation to and from the airport.

SAMPLES COLLECTED

I did not collect any samples during this inspection.

VOLUNTARY CORRECTIONS

I verified corrections to the FDA 483, Inspectional Observations, issued at the last inspection on 03/16/2012. Specifically, I verified the firm put one lot of [redacted] on stability that was manufactured in 2011. I verified this by seeing the Stability Placement Form. I also verified the training of employees with respect to deviations and environmental monitoring. I verified checklists for BPR review were instituted and procedural updates were completed for deviations.

EXHIBITS COLLECTED

Exhibit 1 – List of [redacted] batches shipped since last inspection, 1 page
Exhibit 2 – List of [redacted] batches shipped since last inspection, 6 pages
Exhibit 3 – List of [redacted] Spray Dried Dispersion shipped to U.S., 2 pages
Exhibit 4 – Organizational Charts, 2 pages
Exhibit 5 – Deviation Records Procedure, HQ.CCO.COP014.10.EP, 19 pages
Exhibit 6 – Returned Products Flowchart, 1 page
Exhibit 7 – Risk Assessment Procedure, HQ.CO.SOP105-A1.2.EN, 7 pages
Exhibit 8 – Suppliers Monitoring and Evaluation, HQ.CO.SOP105-A4.0.EN, 4 pages
Exhibit 9 – Statement on Qualification of New Sources, 1 page
Exhibit 10 – Site diagrams, 2 pages
Exhibit 11 – Summary of Calibration Findings, 6 pages
Exhibit 12 – Engineering Dept. Memorandum, 14-ENG-007, 1 page
Exhibit 13 – Calibration and Inspection Record and Delta V Trend, 2 pages
Exhibit 14 – 19WG06-[redacted] Process Flow Diagram, 1 page
Exhibit 15 – 19WG06-[redacted] Process Validation Report Deviations, 10 pages
Exhibit 16 – CRLC4302-FP1: 19WG06-[redacted] Identification, Assay and Related Substances (by HPLC) – Validation Protocol, HQ.QSP.MV572.0.EN, 9 pages
Exhibit 17 – CRLC4302: 19WG06-[redacted] Identification, Assay and Related Substances (by HPLC) – Accuracy Supplemental Protocol, HQ.QSP.MV572-A2.0.EN, 2 pages
Exhibit 18 – CRLC4302: 19WG06-[redacted] Identification, Assay and Related Substances (by HPLC) – Validation Report, HQ.QSR.MV1046.1.EN, 53 pages
Exhibit 19 – Lab Testing Matrix. 2 pages
Exhibit 20 – List of 19WG06-[redacted] Stability Batches, 1 page
Exhibit 21 – 19WG06-[redacted] Bulk Powder – Stability Protocol, HE.SSD.SP151.4.EN, 5 pages
Exhibit 22 – HQ.AA.RX4066: 19WG06-[redacted] Characterization by X-Ray Powder Diffraction (XRPD) – validation report, HQ.QSR.MV1018.0.EN, 15 pages
Exhibit 23 – FDA Wrap up Meeting 25th July 2014, 2 pages

ATTACHMENTS

FACTS Assignment Sheet, Work Assignment ID 9284754 and Operation ID 7278783, 3 pages
Inspectional Assignment (Email Transmittal) Dated July 18, 2014, 11 pages

Brittany D. Ternar, Investigator