DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
629 Cranbury Road
East Brunswick, NJ 08816

May 17, 2013

Mr. David Hoffman, President
US Operations/Vice President – Exclusives Business Unit
Hovione LLC
40 Lake Drive
East Windsor, NJ 08520

MAY 29 2013

Dear Mr. Hoffman,

We are enclosing a copy of the establishment inspection report (EIR) for the inspection conducted at your premises at the above address on April 23rd, 2013 through April 26th , 2013 by Investigator Nicholas Violand on behalf of the U.S. Food and Drug Administration (FDA). When the Agency concludes that an inspection is "closed," under 21 C.F.R. 20.64 (D) (3), it will release a copy of the EIR to the inspected establishment. This new procedure is applicable to EIRs for inspections completed on or after April 1, 1997. For those inspections completed prior to the above date, a copy of the EIR may still be made available through the Freedom of Information Act (FOIA).

The agency is working to make its regulatory process and activities more transparent to the regulated industry. Releasing this EIR to you is part of this effort. The copy being provided to you comprises the narrative portion of the report; it may reflect redactions made by the Agency in accordance with the FOIA and 21CFR Part 20. This, however, does not preclude you from requesting and, possibly, obtaining any additional information under FOIA.

If there is any question about the released information, feel free to contact:

Louise Miranda
U.S. Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, New Jersey 07054
Telephone: 973-331-4903

Sincerely,

Meyer J. Slobotsky
Supervisory Consumer Safety Officer

MJS:gjp
Attachment

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SUMMARY

Routine cGMP inspection of this manufacturer of a single non-sterile active pharmaceutical ingredient (API) was performed as per NWJ-DO FY13 Workplan, under FACTS Assignment 1492660, OP ID 6591993. In addition to campaign manufacturing of this drug substance, the site functions primarily as a research and development site, performing technology transfer activities as a contract service provider for non-marketed drug substances in early-phase development; however, these activities do not fall under the scope of this inspection. Inspectional guidance was afforded through CPGM 7356.002, Drug Manufacturing Inspections; 7356.002F, Active Pharmaceutical Ingredients; and Guidance for Industry titled "Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients."

The previous inspection was conducted 04/27—05/02/2011, and was classified NAI. Coverage of the Quality, Materials, and Production Systems was performed, and the site was found to be solely producing one marketed drug substance, [redacted], for one US customer, [redacted], [redacted]. Although no FDA-483 was issued, the following items were discussed with management at the close of the inspection: fraying of hoses leading to the thermal jacket of one of the glass reactors was observed; failure to remove from service an out-of-calibration CAD detector (attached to HPLC); a laboratory out-of-specification (OOS) investigation was reviewed for two batches that stated no production deviations had occurred, when in fact overmixing had occurred in both batches and was separately documented; and the 2010 Quality Product Review for that fiscal year did not include all of the batches made during that time period.

The current inspection covered the Quality, Production, and portions of the Facilities and Equipment and Laboratory Control Systems. The firm continues to operate as a manufacturer of a single commercial API, [redacted], for the same US customer, with primary operations as a research and development facility for development and clinical phase projects for various customers. Due to previous inspectional history and lack of significant changes in operations, this was performed as an abbreviated inspection. Corrections regarding previous inspectional findings were observed and/or reviewed, with no discrepancies noted. The following items were discussed with management during this inspection: undefined extended timeframes were utilized to identify an unknown impurity and complete an appropriate corrective and preventive action, following an OOS result in an intermediate of the [redacted] process; qualification activities are not performed after moving the ISO-8 hood used for packaging the final product; it is unclear if a validated method allows for contact and settling plates used in environmental monitoring can be inoculated (sampled) and stored at refrigerated conditions over the weekend prior to shipping and incubation by the contract laboratory the following week, as was noted in a deviation report; and the cleaning procedure for the multi-purpose containment hood used to sample the starting material does not adequately address the full range of materials sampled by the primarily R&D facility. No FDA-483 was issued. There were no refusals encountered and no samples were collected.

ADMINISTRATIVE DATA

Inspected firm:	Hovione LLC
Location:	40 Lake Dr East Windsor, NJ 08520-5321
Phone:	609-918-2600
FAX:	918-2615
Mailing address:	40 Lake Drive East Windsor, NJ 08520-5321
Dates of inspection:	4/23/2013, 4/24/2013, 4/26/2013
Days in the facility:	3
Participants:	Nicholas A Violand, Investigator

On 04/23/2013, I, CSO Nicholas Violand, presented my credentials and issued an FDA-482, Notice of Inspection, to Dirce Macário, Head of Compliance **(Att.)**, who stated she was authorized to accept the notice in the absence of David Hoffman, President – US Operations / Vice President – Exclusives Business; and Michael Ironside, Ph.D., General Manager. Later that day, Supervisory CSO Meyer Slobotsky arrived at the facility, and a second FDA-482, Notice of Inspection, was issued to Dr. Ironside, who was then present **(Att.)**. SCSO Slobotsky was present to observe conduct and performance of the inspection, but did not actively participate in inspectional activities. This report was written by CSO Violand.

Official correspondence should be directed to:
David Hoffman, President – US Operations / Vice President – Exclusives Business Unit
Hovione LLC
40 Lake Drive
East Windsor, NJ 08520

CHANGES SINCE LAST INSPECTION

The Establishment Inspection Report (EIR) from the 04/27/2011 et al., inspection details firm history, interstate commerce, jurisdiction, individual responsibilities of personnel that participated in that inspection, the firm's training program, manufacturing/design operations, and discusses procedures for complaint handling and conduct of recalls. A majority of this information remains valid, and there have not been any major changes to the facility and its operations. Details in the 2011 EIR discuss Hovione's corporate headquarters in Loures, Portugal, and other manufacturing, offices, or affiliate sites in China (2), Ireland, Hong Kong, and Switzerland. Hovione's CEO remains Guy Villax, whose primary office is located at the Loures, Portugal site.

The firm continues to manufacture one commercially marketed API for US customer [redacted], also referred to by its finished product code [redacted]. There have been no changes to GMP areas of the facility, equipment, or the manufacturing process for [redacted]. A single laboratory investigation following OOS results for individual unknown impurities in one of the intermediates resulted in clarifications to the associated analytical method; however, conduct of the method was not changed, nor were there changes to any other analytical methods for [redacted] or its raw materials. A majority of the site's operations are related to research and development activities, namely in the area of technology transfer. I asked if any of the tech transfer activities performed were in direct support of filed applications for drug products or drug substances, and Mr. Tomas and Ms. Macário stated they were not. Mr. Tomas discussed these operations are primarily associated with early-phase development projects, with some clinical applications. Major customers for these services are still [redacted], and [redacted], with new customer [redacted] being added since the last inspection.

The performance and tracking of personnel and annual cGMP training remains the same. The content of training, documentation, and tracking mechanism were discussed, with no discrepancies noted. The firm's corporate complaint handling and recall procedures still remain in effect, but there have been no complaints received for the single marketed API manufactured at the facility, nor have there been any recall activities performed. The firm continues to use the same manufacturing codes to maintain accountability of manufactured batches. This consists of a material number (e.g., [redacted]), and a two-part alphanumeric batch number (two letters identifying the facility, followed by a sequential five-digit number generated by the inventory control system, SAP, e.g. NJ00038).

Some changes since the previous inspection, mostly regarding personnel, are summarized below. (Specific personnel changes are also included with the list of personnel that participated in the inspection, provided as **Exh. 1.**):

- Ms. Claudia Ferreira, former General Manager, is now QA Development Director, and Dr. Michael Ironside functions as General Manager
- Dr. Ironside is also the Head of Process Research & Development [noted on the interim organizational chart provided **(Exh. 2, p. 1)**], for which responsibilities were previously held by Mayra Reyes, Head of Process Chemistry
- Ms. Wanda Crumel is no longer Head of Analytical Chemistry, and Ms. Dirce Macário, Head of Compliance, now oversees both Quality Control and Quality Assurance
- Ms. Andrea Cruz is the QA Manager, which was formerly Ms. Filipa Goncalves
- The facility now employs 45 permanent employees (previously 47)
- Annual sales for 2012 were approximately $10.5 million

INSPECTIONAL COVERAGE

This inspection covered the Quality and Production Systems, with portions of the Laboratory Controls and Facilities and Equipment Systems as well. As in the previous inspection, the firm maintains document control via a local procedural system (Site Operating Procedures and Internal Operating Procedures, or SOPs and IOPs, respectively), as well as Corporate Operating Procedures, or COPs. Among these are procedures for managing change control, laboratory OOS investigations, deviations (investigations extending outside the laboratory, to production), complaints, product quality reviews, auditing of suppliers and contract service providers, and other Quality Unit functions. An overview presentation of quality systems at the East Windsor facility was provided as **Exh. 3.** A process overview was provided as **Exh. 4,** showing each process step, the intermediate it produces, the type of equipment used, typical batch size, and special handling considerations for the potent finished product. A facility diagram shows three small Class 100,000 areas, the first of which is used to produce [redacted] **(Exh. 5).** Coverage of Quality and Production Systems are described below, with portions of the Facilities and Equipment and Laboratory Control Systems included (see **Changes Since Last Inspection** for discussion of Quality System functions that remained the same):

- A listing of the intermediate and finished product lots generated since the last inspection was provided as **Exh. 6.** Product code [redacted]020 is the first intermediate produced, [redacted]035 is the second intermediate, [redacted]040 is the final intermediate prior to crystallization, and [redacted] is the finished product. During the inspection, three specific lots of finished product, lots NJ00036 through NJ00038 were observed in the warehouse and were awaiting release, but no actual processing of [redacted] was being performed. Representative batch records for the finished product and intermediate [redacted]035 (noted in **General Discussion with Management** to have had an issue with the analytical test for individual unspecified impurities) were audited for documentation and control of critical process parameters and documentation of performance for each step. Mr. Tomas discussed that multiple batches are produced campaign-style and stored until the next process step, and each has a validated hold time (e.g., six to twelve months). I observed that re-testing of in-process material that has been on hold is performed prior to the next process step, to ensure appropriate quality. Cleaning procedures were discussed and reviewed, and it was found that detailed instructions were available for all equipment, with photographs of specific areas requiring assembly of CIP systems or disassembly.

- As the finished drug substance is sold to the customer for use in a sterile product, controls were observed to filter many liquid components used in downstream processing through 0.2µ filters, to remove potential bioburden (filter integrity tests documented). The ISO-8 processing room includes a containment hood to protect the operator from the potent material, along with specific gowning, the level of which varies depending on the process step. Although demineralized and purified water are specified in filed process steps, Mr. Tomas demonstrated that higher quality (purchased) water is used for many steps (increase from demineralized water to purified water, and purified water to water for injection).

Quarterly environmental and personnel monitoring data was also discussed and reviewed with Ms. Macário, which included settling plates in the ISO-8 processing area and hood used for packaging, as well as operator contact plates. Data since the last inspection, along with a historical data review were covered, with all data points remaining within the established alert limits.

- An example of a finished product label and shipping label were collected as **Exh. 7.** As each intermediate lot has its own unique lot number, I asked for Mr. Tomas to demonstrate the traceability of the intermediate lots that were used in finished product lot NJ00037, which is included as **Exh. 8.** It includes three lots of intermediate [redacted]040, and the lineage of each prior intermediate batch back to the starting material ([redacted]) is shown.

- An audit of laboratory data, alongside the review of intermediate and finished product batch records, was performed for selected lots of [redacted]035 and [redacted], with the assistance of Nuno Rodrigues, Release Group Leader. All details regarding sample preparation, testing, calculations, and final results are recorded in dedicated controlled notebooks. Sufficient details for analyses such as impurities by HPLC and water content were observed in the notebooks, along with second-person check of all data and critical steps of analysis. The finished product specification **(Exh. 9)** and a finished product certificate of analysis for lot NJ00031 **(Exh. 10)** are included. A walkthrough of the QC laboratory found it was broken into GMP areas for testing of [redacted] and R&D, which were clearly separated and had dedicated equipment. Samples are delivered by production personnel, and logged in for testing into LIMS with an auto-generated sample number. Controls regarding reagents, buffer/mobile phase solutions, chromatography columns, and reference standards were discussed and reviewed, with no discrepancies observed. Sample solution stability has been established for chromatographic tests; and in the event of a discrepancy or out-of-specification, analysts begin their investigation as quickly as possible, within sample solution stability whenever possible. Examples of qualification of in-house reference standards were also covered, as were the equipment qualification and calibration programs. One piece of equipment was noted as being out of calibration, but was clearly marked as out of service until calibration is performed. Control of electronic data in the laboratory from chromatographic systems included individual sign-on, auto-save to a remote server, daily back-up of data by personnel outside the laboratory, audit trail, and prevention from file deletion or alteration. There were no significant changes to any analytical methods since the previous inspection, and no subsequent validation activities had been performed. An investigation into an out-of-specification result for individual unknown impurities in a batch of [redacted]035 was found to be only partially investigated by the time retesting was performed as per the OOS procedure, with passing results obtained. The unknown was not identified until several months later, and the clarification to the method to prevent future incidences was not made until more than a year after the initial OOS result. See **General Discussion with Management.**

- Product quality reviews for 2011 and 2012 were reviewed, and no discrepancies were observed. They included trending of yields and release data, and compared current-year information to averages from prior years. Other information, such as deviations, OOS results, equipment, and change control documents were included. I noted that process yield at each phase was presented as a graph, and discussed that presenting other information such as process related impurities can help illustrate whether each step of the process is remaining within a state of control (presented in a table). Although there is a relatively small data set for each year's report, Ms. Macário agreed.

- Laboratory OOS investigations and deviations were reviewed (noted above), and an issue regarding timeliness of completion of corrective and preventive actions was encountered, see **General Discussion with Management.** There were three deviations since the previous inspection, and one laboratory OOS report, the latter of which was found to be due to a sample preparation error and was overcome.

- Stability testing is not performed at the site, but is performed by the customer, [redacted]. I discussed with Ms. Macário that this data is still valuable and critical to the operations performed at Hovione, as it can be an indicator of sufficient or insufficient process control. Stability data for all lots currently on accelerated and long term programs was collected as **Exh. 11.**

- All associated change requests initiated for [redacted] were reviewed electronically, and these were all editorial or clarification updates to procedures. There were no process or analytical changes since the last inspection.

- There were no additional process or method validation activities performed since the last inspection.

- Evaluation of contract service providers and raw material suppliers was discussed. New suppliers are evaluated first using a paper questionnaire which includes evaluation of quality systems and controls in place. The site's FDA registration and previous inspectional status are also considered; and a site audit by Hovione is performed once approximately every three years. Lists of approved material suppliers, contract service providers (laboratories) with audit plan, and other contractors (re-certification of ISO-classified areas and calibration of instruments) is included as **Exh. 12.** No discrepancies were observed regarding evaluation and approval of these suppliers/service providers.

Corrective actions regarding discussion items from the previous inspection were discussed and/or covered during this inspection. For example, the hoses leading to the jacket fitting on one of the glass reactors was observed to be frayed. Although this did not have product contact, general equipment maintenance to ensure proper function was discussed, and the hose had been replaced. I

did not observe any similar discrepancies during the current inspection; however, all of the process equipment was covered and stored in the warehouse area, with only portions of the equipment visible. While in the laboratory, the previous inspection found an out-of-calibration CAD detector, attached to an HPLC system. Although it was described as not being used for [redacted] procedures were updated to clearly mark equipment that was out of calibration. An example of this was observed during a walkthrough of the QC laboratory. A discrepancy regarding a laboratory investigation was observed during the previous inspection. It stated that no production deviations had occurred, when in fact overmixing had occurred, and was separately documented. No such observations were seen during the current inspection; however, a significant delay was seen in fully investigating and generating an appropriate preventive and corrective action. See **General Discussion with Management.** The previous inspection found that not all batches produced during the fiscal year were included in the product quality review; however, Ms. Macário discussed that intermediate batches are not included, as a large portion of the review includes yield and completion of the entire process. She stated that these are included in the next year's review, as part of a complete process.

GENERAL DISCUSSION WITH MANAGEMENT

The below items were discussed with management during the inspection and again at the exit meeting held on 4/26/13. At that meeting, the following personnel were present for discussion:

- David Hoffman, President – US Operations, Vice President Exclusives Business Unit
- Michael D. Ironside, Ph.D., General Manager
- Dirce Macário, Head of Compliance
- Filipe Tomas, Head of Process Engineering
- Nuno Rodrigues, Release Group Leader
- Andrea Cruz, Quality Assurance Manager
- Dhvanit Patel, Process Engineer

1. While covering laboratory OOS investigations and deviations/investigations relating to production, I noted a discrepancy among one of three deviations reviewed (which was associated with the only OOS investigation initiated since the previous inspection). A suspected OOS (11/01/2011, OOS11.006) was confirmed 11/11/2011 for intermediate [redacted]035, lot numbers NJ00027 and NJ00028, as well as lot NJ00025, which was being re-analyzed during its hold period prior to the next processing step. These three lots were above the limit of NMT 2.0% for major unspecified impurity (2.2 – 3.7%). A fourth batch, lot NJ00026, was also being re-analyzed, and was higher than historical values, but within specification (1.2%). (All of the associated documents for this discussion item are **Exh. 13**).

   No errors were initially found during analysis, nor were any issues found during production

(Deviation 13458). Further subsequent investigation into the analysis found an issue with the water bath level during sonication, which was suspected to be causing the unknown impurity (which at that time was still unidentified). Additional investigational testing into the sonication issue was performed. Re-testing from the original pulled sample (three new sample preparations from each) was performed as per the OOS procedure, and all levels were found to be lower and well within specification (all four lots were retested, with average values of 0.5% to 1.0%). Two of the samples were dissolved by swirling only, and the other two were dissolved by closely monitored sonication, checking for dissolution each minute. This testing was completed 12/2011, and the OOS was overcome, but the deviation report noted that additional investigation was still necessary, under a CAPA (14375).

The impurity was later identified using in-house LC-MS/MS; however, this was not performed until approximately 08/2012, nearly 9 months after the initial OOS. It was found to be an additional reaction product that results when acidic conditions (part of the manufacturing process) and additional heat/energy are applied. The additional heat/energy were associated with the low water level during sonication; and as a result, a limit in the method was placed on water level. The method update was not completed until 02/2013, nearly 15 months after the initial OOS.

I discussed with Ms. Macário that investigations and subsequent corrective actions should not remain open for unnecessarily long periods of time. It was taken into consideration that [redacted] is produced in small batches [redacted] and in infrequent campaigns (twice annually); however, I discussed that the identification of the unknown impurity should have coincided with the initial investigation. This should not have been delayed, even though incorrect sonication was known as the likely root cause upon retesting. In addition, once a corrective and preventive action could be established, to set a limit on the water level in the sonicator (noted as per equipment manufacturer's recommendation), there should not have been such a delay for the method to be clarified and updated. I discussed that the procedures for laboratory and production investigations, as well as CAPAs, should have clearly defined steps for extending past their initial due dates (set at 30 days for investigations). These should include management approval for extension, and due dates for the extensions. All other investigations and CAPAs reviewed were completed within their established timeframes. Ms. Macário, Dr. Ironside, and other management present stated their understanding of this discrepancy. Dr. Ironside promised a written response to New Jersey District within 15 business days addressing all discussion items.

2. Setup and verification activities are performed for all of the mobile equipment used for production of [redacted], which primarily consists of small-scale glass reactors and filter-driers. The final piece of equipment used is an ISO-8 containment hood used for packaging of the finished material, for which the verification activity includes checking for cleanliness, but no functional verifications. I discussed the expectation that a qualification activity be performed whenever a piece of equipment is moved, which is the case for all of the equipment for [redacted] (moved from locked area of controlled warehouse to controlled

processing room). While such verifications are part of the routine process for the reactors and filter driers, this is not the case for the hood. I further discussed that adding an additional check for overall condition of fragile equipment, such as glass reactors, can provide valuable information in the event a chip, break, or other damage is discovered during production. Upon review, it was found that re-certification of the ISO-8 hood is performed every 6 months, in the same manner in which the hood is used (i.e., it is rolled out of storage and relocated before re-certification). Air settling plates are also collected during each campaign, to support operation of the hood. Mr. Tomas and Ms. Macário stated their understanding, and that they would add functional and overall condition checks to pre-existing setup and verification forms, focusing on the ISO-8 hood for packaging. Dr. Ironside promised a written response to New Jersey District within 15 business days addressing all discussion items.

3. Deviation Report 10459 was issued following the discovery that the contact and settling plates used for environmental monitoring had been read shortly after the expiry dates of the plates (samples had been collected prior to expiry). This was due to an unexpected delay in production, which resulted in collection of samples on a date later than expected. The firm's contract laboratory performing microbiological testing, [redacted] (now [redacted]), provided the plates to Hovione, and they were sent back for analysis after collection for incubation and reading.

   The specific deviation was adequately addressed; however, I noted that the samples were collected on a Friday afternoon, and were placed at refrigerated conditions until they could be shipped back to [redacted] the following Monday. Dr. Ironside noted that this was done with the knowledge of the contract laboratory; however, I discussed that it is Hovione's responsibility for ensuring this practice is valid. While a positive control is run alongside the samples, I discussed that the firm should ensure that storage at refrigerated temperatures for over 24 hours prior to incubation did not affect the viability of the organisms present at the time of collection. Hovione should ensure that the contract laboratory has sufficient data to demonstrate adequate recovery following refrigeration for at least this duration, prior to incubation. Dr. Ironside, Ms. Macário, and Mr. Tomas stated their understanding, and that they would contact the laboratory to further discuss this issue. Dr. Ironside stated they may also change internal procedures such that samples are no longer collected on Fridays. He also committed to submitting a written response to New Jersey District within 15 business days regarding all discussion items.

4. Incoming raw materials for [redacted] and R&D materials are sampled in a shared HEPA-filtered hood in the sampling/dispensing room (unless considered to be a potent compound, which is done in a separate designated area). The cleaning procedure for the hood tells the operator to use water, or acetone if necessary, to remove traces of the previously weighed material (done after each material, in between weekly and monthly full cleaning of the hood and the room, respectively).

I discussed that the instructions should be more specific, and should address which solvent to use for which type of material; however, Mr. Tomas noted that since the facility performs primarily R&D functions, many different materials are sampled and weighed in the hood, and it is not possible for the procedure to address all of them. I discussed evaluating the effectiveness of acetone for the removal of the most difficult-to-clean material used in this hood; and that if the operator is to consult with a supervisor for further instruction, this should be clearly indicated in the procedure. Mr. Tomas and Ms. Macário stated their understanding, and that they would update the procedure. Dr. Ironside promised a written response to New Jersey District within 15 business days regarding all discussion items. I noted that this is the only portion of the process for [redacted] that uses a multi-purpose room or area. All equipment is dedicated, and any tools coming into contact with materials or product are disposable.

EXHIBITS COLLECTED

1. List of personnel that participated in the inspection, and personnel changes since the last inspection, 1 pg.
2. Interim organizational chart and previous organizational chart, 2 pgs.
3. Overview of quality systems at Hovione East Windsor site, 7 pgs.
4. Manufacturing overview and process flow diagram for [redacted], 11 pgs.
5. Facility diagram, 1 pg.
6. List of batches produced since the previous inspection, 2 pgs.
7. Representative product label as applied to finished container, as well as shipping label, 3 pgs.
8. Example of traceability of intermediate batch numbers to finished drug substance batch, 3 pgs.
9. Finished product specification for [redacted], 2 pgs.
10. Finished product certificate of analysis for lot [redacted].NJ00031, produced January 2012, 1 pg.
11. Stability summaries for all lots on stability, accelerated and long-term (as performed and provided by customer [redacted]), 43 pgs.
12. List of approved suppliers, approved contract laboratories with audit schedule, and organizations providing contract services (calibration of equipment and qualification of classified areas), 4 pgs.
13. OOS11.006 and deviation report 13458, regarding individual unknown impurity in intermediate [redacted]035, 19 pgs.

ATTACHMENTS

1. FDA-482, Notice of Inspection, issued 4/23/2013, to Dirce Macario, Head of Compliance (in absence of general manager and president), 3 pgs.
2. FDA-482, Notice of Inspection, issued 4/23/2013, to Michael Ironside, Ph.D., General Manager, to add SCSO Meyer Slobotsky to inspection (for observation only), 3 pgs.

Nicholas A Violand, Investigator