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

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December 12, 2013

Mr. Guy Villax
Chief Executive
Hovione FarmaCiencia SA
Sete Casas
2674-506 Loures, Portugal

Reference: FEI 3002807208

Dear Mr. Villax:

We have completed our review of the Establishment Inspection Report (EIR) for the inspection conducted at your active pharmaceutical ingredient manufacturing facility in Loures, Portugal by Investigator Yumi J. Hiramine during the period of September 23 - 27, 2013.

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 practice (CGMP).

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,

Temeka Moore for

Alicia Mozzachio
Branch Chief
Division of International Drug Quality

Enclosure: EIR

Establishment Inspection Report	FEI:	**3002807208**
Hovione FarmaCiencia SA	EI Start:	09/23/2013
Loures, Portugal	EI End:	09/27/2013

TABLE OF CONTENTS

SUMMARY

This was a cGMP Inspection conducted utilizing Compliance Program, 7356.002F, Active Pharmaceutical Ingredients Inspections. In addition, this was a Post-Approval Inspection, utilizing Compliance Program 7346.843, Post-Approval Audit Inspections, covering [redacted]

Establishment Inspection Report	FEI:	**3002807208**
Hovione FarmaCiencia SA	EI Start:	09/23/2013
Loures, Portugal	EI End:	09/27/2013

This inspection was covered under FACTS Assignment ID: 8684137. Profile Classes CSN – non sterile bulk by chemical synthesis. EES notes that for [redacted], the site is profiled for CSN and TCM. However, it was confirmed that the firm does not manufacture tablets for commercial use, only for R&D purposes. The site only manufactures the API for this NDA.

Hovione FarmaCiencia SA is a manufacturer of both medical devices and drugs. The previous FDA medical device inspection was conducted from 2/25/13 – 3/1/13 and was a Medical Device Post Market inspection for PMA [redacted] Propel Sustained Release Therapy. Hovione is considered as a manufacturer of a component of a medical device. No FDA 483 was issued to the site. Medical Devices were not covered during this inspection.

The previous FDA drug inspection was a Pre-Approval of a foreign manufacturer of active pharmaceutical ingredients (API) and spray dried dispersion (SDD) intermediate conducted under The inspection covered the firm's manufacturing processes and included review of the Quality, Production, Facilities & Equipment, Materials and Laboratory Systems for [redacted] and [redacted] No FDA-483 was issued to the site, however there was a Discussion with Management. *Refer to Voluntary Corrections in this report.*

The current inspection evaluated the Quality and Laboratory Controls System. Limited areas of inspectional coverage included Production, Materials, Facilities and Equipment, and Packaging and Labeling Systems. No Inspectional Observation Form FDA-483 was issued to the firm, however there was a Discussion with Management.

The firm is inspected by the Regulatory Health Authorities to include EDQM (European Directorate for Quality of Medicines & Healthcare), KFDA (Korea) , INFARMED, PMDA (Pharmaceutical and Medical Devices Agency (Japan), IMB (Irish Medical Board) and U.S. FDA. In addition, the firm has a current drug registration in eDRLS.

There were no refusals and no samples were collected.

ADMINISTRATIVE DATA

Inspected firm:	Hovione FarmaCiencia SA
Location:	Sete Casas 2674-506 Loures, Portugal
Phone:	351 21 982 9381
FAX:	351 21 982 9498
Mailing address:	Sete Casas 2674-506

	Loures, Portugal
Dates of inspection:	9/23/2013, 9/24/2013, 9/25/2013, 9/26/2013, 9/27/2013
Days in the facility:	5
Participants:	Yumi J. Hiramine, Investigator

Credentials were presented to Mr. Nuno Durarte de Almelda, Site Manager who introduced himself as the most responsible person on-site at the time of this inspection. Mr. de Almelda explained Guy Villax, CEO was out of town on a business trip for the week.

FDA correspondence including FMD-145 should be addressed to:

Guy Villax – Chief Executive
Hovione FarmaCiencia SA
Sete Casas
2674-506 Loures, Portugal
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U.S. Agent

Ms. Dirce Macário, Head of Compliance TTC
Hovione, LLC
40 Lake Drive East Windsor
New Jersey, 08520
Telephone: (609) 982-9000 or (866) 918-2601)
Fax: (609) 918-9388
Email: dmacario@hovione.com

HISTORY

Hovione FarmaCiencia SA is part of Hovione Holding Limited. The company was founded by Ivan Villax, Ph.D. in 1959 and the first plant was built in Loures, Portugal in 1969. The company has manufactured commercial active pharmaceutical ingredients. The Loures, Portugal location has been inspected by FDA several times, with the first inspection being conducted in 1982. In addition, in 2011 the FDA conducted a QBD inspection.

Hovione has four business units to include Exclusives (i.e.: R&D, process validation, PAR studies, clinical API supply), Inhalation (i.e.: formulation/device development, powder characterization, morphology analysis), Particle Design (i.e.: spray drying, freeze drying, micronization, and milling) and Generics (i.e.: APIs, tetracyclines and corticosteroids). Total sales in 2012 were $184 million USD.

Hovione FarmaCiencia SA, Loures Portugal site is considered the Headquarter site and encompasses approximately 37,300 square meters. The plant consists of 15 multi purpose buildings/blocks.

In addition, Hovione has multiple locations globally to include sites in China (Macau, Taizhou, Shanghai), Ireland (Cork), and the U.S.(New Jersey). Hovione ships drug products globally to main markets in North America, Europe, Japan, Australia and New Zealand.

The firm operates 24 hours a day, 7 days a week in two or three shifts with four teams. There are approximately 630 employees on-site to include: 42% Production, 17% R&D, 14% Administration, and 6% QA/Compliance.

INTERSTATE COMMERCE

Hovione FarmaCiencia SA is approved to manufacture the following APIs to the U.S.:

- [redacted] Spray Dried Dispersion [redacted]
- [redacted] Spray Dried Dispersion [redacted]

These APIs are directly shipped [redacted] or shipped to [redacted]

Mrs. Paulo provided a list of all products manufactured at the site (***Exhibit YH #1***), and a list of DMF/VMF products (***Exhibit YH #2***).

JURISDICTION

Mrs. Paulo provided a list of U.S marketed products shipped to the United States to include the material name, batch #, quantity, customer and address shipped to, and delivery date (***Exhibit YH #3***).

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Key Management at this site include:

Guy Villax, CEO – is the son of the company founder and is the most responsible person on-site.

Nuno Duarte de Almelda - Site Manager has been in this position for 6 years.
Luisa Paulo - Compliance Director has been with the company for 30 years.

José Lisboa – Quality Assurance Director has been with the company for 30 years.

Joana Ferreira – Head of Quality Systems Management has been with the company for 16 years.

Joana Mateus – Head of QA Drug Products, Technical Operations has been with the company for 14 years.

Filipe Rosa Vicente – General Manager, R&D – Lourdes

Other personnel who provided information during this inspection include the following:

Rui Teixeira – Head of Production Line

David Martins – Production Director, API

Noé Carreira – Vice President, Technical Operations

Daniel Monteiro – Technical Expert, Manufacturing

Luis Rato – Technical Expert, Manufacturing

Luis Sobral – Senior Chemist, Group Leader, R&D

Elisabeth Mateus – Senior Chemist, Group Leader, R&D

Albino Carvalho – Team Leader, Warehouse

Manual Carvalho – Warehouse Coordinator, Logistics

Hugo Galaio – Director of Logistics

Alvaro Lopes – Head of Production, Exclusives
Jorge Guerreiro – Director R&D, Engineering

José Ascensão – Production Director, Drug Product

Jorge Valadas – Head of QA, Drug Substance

Nuno Rebelo – QA Technical Expert

Teresa Barão – Head of Qualification & Validation

Aldo Vidnha – Qualification Technical Expert, Engineering

Alexandra Silva – Director of Quality Control, Production

Mónica Barreto – QC Technical Expert, Microbiology

Cristina Silva – QC Technical Expert

Joana Azuaga – QC Assistant Technical Expert

Fernanda Rodrigues – QC Sampler

Ricardo Gariso – QC Assistant Technical Expert

Irina Rodrigues – QA Technical Expert

Rui Estrela – QA Technical Expert

Mrs. Paulo explained there are have been no changes to management since the previous FDA inspection. In addition, Mrs. Ferreira provided a copy of the organizational charts of Hovione FarmaCiencia SA to include the Hovione Group, QA Development, QA Technical Operations, and QC Production Area as ***Exhibit YH #4***.

FIRM'S TRAINING PROGRAM

The written procedure, "Training", Document Ref.CCO-COP.007.4.EP, Version 4 Effective date: 3/15/13 was reviewed.

There is a Job Competences Matrix for each new employee. Each matrix identifies the skill requirements and has to attend training sessions. This is defined by the Department Supervisor. Each training session has an evaluation (pass/fail). This includes the training sessions for the qualification process and competence required. An Individual Training Plan is also developed. New employees have basic training to include policies, cGMPs, health and safety training.

The firm uses a training management system called TrainStream. All training documentation is within this system. For example, within the Production department, the operator can be qualified by taking the e-test in TrainStream and manual qualification (OJT) with practical skills.

Annual review of the training needs of the employee is evaluated and reviewed with the Supervisor. Re-training could include SOP modifications or changes in processes.

GMP training involves different departments that are issued different modules dependent on responsibilities. There are classroom, practical workshops, and e-learning modules. The Compliance Department is involved in developing the GMP training, and is responsible for the training that is performed. HR will monitor the training.

GMP training for 2013 was reviewed with no issues observed. In addition, the training records for Production Operator, "MDS" and QC Analyst "JSO" were reviewed with no issues observed.

MANUFACTURING/DESIGN OPERATIONS

[redacted]

Mrs. Paulo explained that [redacted] was approved in January 2012 by the FDA, as notified by [redacted] NDA holder. An FDA site inspection was not conducted for this approval. Thus, this product was covered during this inspection.

The drug intermediates, API and drug dispersion of the API are conducted at Hovione FarmaCiencia SA. The intended use of the finished drug product is to be used in the treatment [redacted]

There are four steps for the synthetic route that are conducted to manufacture [redacted] include:

- Step A: [redacted] is added with [redacted]

- Step B: [redacted] is added with [redacted] to form [redacted]

- Step 1: The addition of Step A + Step B, with [redacted] to form the non-isolated intermediate, [redacted]

- Step 2: Excipients are added to the non-isolated intermediate to form [redacted]

After the manufacture of the API, it goes through the Spray Drying Dispersion process (known as SDD). The API [redacted] is added [redacted] additional solvents go through a spray drying process. The product is transferred to the post drying step (a 2nd drying process in a double cone dryer to reduce the residual solvents). The [redacted] spray dried dispersion [redacted] Once dried, the product is packaged, weighed, and labeled.

MANUFACTURING CODES

Manufacturing codes are assigned within the firm's SAP system. For example, Lot# 19QB07019 represents:

First two digits represents the group number (i.e.:19 = drug product, 17 = API, 16 = exclusive product)

Two Letters represents the customer code [redacted]

Next two digits represents the sequential number of the batch [redacted] manufactured for the customer)

Last digits represents the type of product (i.e.: 19 = Spray dry dispersion)

QUALITY SYSTEMS

Product Quality Review

The written procedure entitled, "SOP - Quality Management – Product Quality Review", Document Ref: HQ.CCO.COP006.1.EN, Version 1, Effective Date: 1/15/11 was reviewed, however there is no timeframe for completion. ***Refer to Discussion with Management, Issue #5.***

QA with the assistance of other departments is responsible for writing the PQR. The final approval is conducted by the Site Manager.
The following PQRs were reviewed with no issues observed:

- "17QB01 [redacted] - 2012 Product Quality Review", Document Ref: HQ.QSR.AR117.0EN, approved on 6/22/13
- "17QB07 [redacted] – 2012 Product Quality Review", Document Ref: HQ.QSR.AR123.0.EN, approved on 9/22/13

Mrs. Feirreira explained there was no 2011 PQR Report written for this product since no batches were manufactured.

Change Control

Changes are documented in a computerized system called ChangeStream. All changes are placed into the system by QA/QC or Technical Expert. The person who places the change into the system is the responsible for the change and describes the purpose, justification and lists all the tasks that need to be performed and who is responsible for each task. The classification is conducted by all relevant departments. If it is a major change, then the Department Head must also approve the change. QA has to evaluate and approve each change. As each task is completed, it is documented in the system in the appropriate CC number.

The issuer of the change will check to see if it was completed and effective. The change will go to QA for the final approval and closure of the change and will also review the effectiveness of the change.

The following changes were reviewed:
CC HQ 4582 change to the PW system SPAP02 was requested (major change) of the PW feeding line between the Ultra filtration system (UF650) and PW sampling point SP60511 prior to storage tanks TA39/T650.

CC 4144 was issued in order to establish an adequate sample volume and assess alert/action limits for Sampling point SP605011.

Rejects

The storage of rejected products is located under lock and key in the Warehouse. There was a rejected lot of the excipient, Potassium Carbonate, Lot #100432.HQ00017that was observed during

the walk through. The record, Ref Doc HQ.QSD.RF586.1.PO, documents the location (area #15), the seal used with ID recorded, the product, lot#, and the weight of the product. The product is going to be destroyed off-site. No issues were observed.

Stability Failures

There was one confirmed OOS for stability reported as Deviation# 27354 and also reported as a Field Alert Report. *Also refer to Field Alert Report section of this report.* This was reported for the [redacted] for the 24M stability time point that occurred on 5/30/13. The deviation report was created on 6/4/13, on HPLC76.

This occurred for the analysis of sample, [redacted]. An investigation was performed in the lab and QA was notified 6/7/13. The OOS report determined the root cause as analytical error.

The investigation found that there is a deficiency in the Sonicator equipment used in the QC lab and different practices by the analysts used during the sonication operation. CAPA #28776 was issued to perform the assessment of maintenance/qualification process of the Sonicator. In addition, the Sonicator was replaced. CAPA #28964,#28965 and #28966 was issued to assure that QC labs (AA – wet chemistry analysis, CR – chromatography lab, MI – microbiology) teams were informed about best practices to use for the Ultrasonic Bath Equipment. Since that time, there have been no other issues with the sonicator.

Field Alert Reports

There was one Field Alert Report reported by the NDA holder [redacted] regarding the routine stability testing conducted at 24M [redacted] for assay at the 24M. Result from the Sample 1 was 89.0% and Sample 2 was 97.6% where the specification is between 95% - 105%. This was also documented as Deviation Deviation# 27354.

The initial FAR was reported to [redacted] FDA office on 7/10/13 (***Exhibit YH #5***). An investigation is continuing to determine the root cause.

A follow up FAR was submitted on 7/25/13 to FDA stating investigation to date indicates the problem resulted from analytical error (***Exhibit YH #6***). Specifically, the root cause was determined during the sample preparation using the sonicator, such as sonication placement of the samples and duration of samples are in the sonicator, as well as the and hold times of the samples prior to analysis. As a CAPA, more detailed sample preparation procedures are proposed to address sample dissolution, including acquisition of a new sonicator and assessment of sonication time and sample hold time following sonication.

A follow up FAR was submitted on 8/15/13 to FDA to provide further information (***Exhibit YH #7***). The root cause is inadequate sample dissolution during sample preparation. Testing of the sonicator confirmed that one position was not operating properly and this likely contributed to the dissolution issue. The acquisition of the sonicator is ongoing. Once received, a retest plan will be executed.

A Final FAR was submitted on 9/23/13 to FDA to provide further information (***Exhibit YH #8***). A new sonicator was acquired. Qualification and maintenance program for the sonicators will be defined. In addition, CAPA# 28337 is the acquisition of a new Sonicator. It was decided that run the retest analysis of the new equipment for the original OOS result [redacted]. New one was purchased, Branson 800 (US12) was qualified prior to use. An operational verification test report was issued as HQ.QSR.EQ282.

Re-test plan was defined and retest plan using 3 retests (each retest comprising of 2 sample preparations for a total of 6 preparations) using the new Sonicator. All retests were in specification and shows similar results. As a result, the lot was released.

As a Preventive Action, other laboratories on-site as well as other Hovione sites were informed of the potential issue with the sonicator baths. The firm is still in process of determining best practice for analysts to either keep the flasks in one location or to rotate them.

Deviations

The procedure entitled, "Deviation Records", Document Ref: HQ.CCO.COP014.10EP, Version 10 Effective Date: 2/21/13 was reviewed.

The CAPA database is the computer system used to record, monitor and track deviations. There are people assigned in each department that will place the deviation into the CAPA system, then notification to close the deviation.

Deviation is considered as incidents or not normally expected. There are different types of incidents to include quality incidents, software incidents, QC incidents (analytical), and VQ incidents (Validation Qualification).

There are 3 types of CAPAs:
Correction = immediate corrective action
Corrective action = action to eliminate the cause of the deviation (may take longer)
Preventive action = action taken to eliminate the cause of the deviation

The responsible person who reports the deviation (issuer) and QA can close the deviation. For QC related deviations, the designated QC person can close the deviation. Timeframes for completion of a deviation is not more than 30 calendar days.

The following deviations were reviewed with no issues observed:

Deviation 22205, dated 9/19/12

[redacted] using Discharge System - DDS101

Foreign particles were observed during the collection of the homogeneity samples. The root cause was determined the as the Autosampler itself. An investigation was performed to include a comparison with the foreign particles and the particles generated from the teflon from the Autosampler which was identified and confirmed. The testing and confirmation was reported in, "Report RAMAN Microscopy of Particles Found in Ivacaftor Drug Product" conducted by Sovias AG, in Switzerland, dated 10/30/12. No issues were observed.

During the investigation, no foreign particles were observed in the drums, sieve, and train of equipment. Other lots were reviewed that use this device and no similar issues were reported in the batch records. No particles were reported [redacted] As a CAPA, the firm is no longer using the Autosampler. An assessment was conducted and there is no quality impact to the product. In addition, a toxicological assessment was performed by [redacted] Drug Safety Evaluation Toxicologist. Preventive action is to evaluate a new solution for sampling. Currently, manual sampling is conducted throughout the discharge.

The batch was released since it was determined that the particles were confirmed to have only come from the Autosampler while taking samples for testing.

Deviation #21726

Water sampling points PU21 and PU23 have a lower performance

Water sampling points PU21 and PU23 have a lower performance when comparing to other use points, therefore CAPA #15254 was issued to improve the performance. CAPA includes daily purge of each point use (due to low frequency usage), which was implemented 3/2012. This CAPA was considered effective since there was trending conducted from June – December 2012 with results in specification.

Quality Agreements

The Quality Agreement [redacted]
Document Number QAgr-0005, Version 6, dated 6/12/11 was reviewed with no issues observed.

COMPLAINTS

The written procedure entitled, "Handling of Complaints", HQ.CCO.COP029.5EN, Version 5, Effective Date: 9/10/13 was reviewed.

Complaints are entered into the CAPA system database that is shared with all Hovione sites. Complaints are received usually as an email or letter and QA will be informed of the issue. A Complaint Team is formed with QA and relevant departments. The client will be informed that a complaint has been received and assigned an internal number.

An investigation will be conducted and documented in the Investigation Report to include information, actions, investigations, conclusions, and if root cause found and if impact to quality. Client has an opportunity to provide feedback based on the investigation. Once the complaint report has been agreed upon, the CAPA system has the acknowledgement of the client acceptance and QA will close the complaints. Timeframe to complete the investigation is within 30 calendar days dependent on the nature of the complaint. Once the complaint is closed, the complaint report will be issued to the client.

The following complaints were reviewed:

Complaint 13951
Foreign matter found on SDD
Date received: 11/28/11

The complainant stated that atypical foreign matter was found in one drum of the lot. Investigation started and team meeting occurred with the customer. The customer provided the results of the IR spectra to Hovione. The foreign matter was analyzed and confirmed as a component of the API. The sequence of batches prior to were reviewed with no discrepancies. A definitive root cause could not be confirmed. The firm conducted a study with the API to determine if segregation/stratification could occur during formulation, however the stratification could not be concluded. There were no CAPAs specified and was considered an anomaly.

Complaint 12982: *API*
Unknown peaks in Residual Solvents testing for 7 lots
Date: 10/24/11

The customer found unknown peaks in Residual Solvents testing during their incoming raw material analytical testing. This includes the following batches supplied to the customer

An investigation was performed. The Hovione GC method only as a signal to noise ratio up to 10, whereas the customer has a quantitation limit below 10 (signal to noise ratio), which did not pick up the unidentified peaks.

The client identified the unknown peaks as hydrocarbonate chains, a derivative of heptane or octane (methyl, ethyl, or propyl). However, API/intermediates do not use derivatives of heptane or octane. No octane is produced where the product is manufactured. The solvents used in the process . A study was performed and it was determined that the unknown peaks appear only during the micronization step. The chemical batch does not have any detection of the unknown peaks. Compressed air is used in the room during the micronization process and there is a level of oil vapors/aerosols present, however meets the requirements of DIN ISO8573-1 for air class 2. The compressed air was analyzed and confirmed that the oil is made up of the carbonate chains, thus root cause was determined. As a CAPA, an additional air filter was installed in the air compressor that feeds the micronization room, and changing of the filters every 3 months. To optimize the micronization process, a maximum of 2 micronization steps will be conducted, since previously there was no limit defined. As a preventive action, the firm is going to install an oil free compressor and install a Malvern particle size analyzer that will continuously monitor the particle size to be purchased by end of 2013. However, there is no CAPA assigned to this activity. Refer to ***Discussion with Management, Issue #3***.

RECALL PROCEDURES

The firm has a procedure entitled, "Product Recall". HQ.CCO.COP030.1.EN , Version 1, Effective Date: 3/10/11 that was reviewed.

For U.S. recalls, the NDA holder is responsible for the notification to the FDA, as well as monitoring, and closing of the recall. However Hovione, as the API manufacturer will assist as needed.

Mrs. Mateus and Mrs. Ferreira both verified there have been no recalls at the facility.

FACILITIES AND EQUIPMENT SYSTEMS

Equipment

Cleaning Procedures of Equipment

The written procedure entitled, [redacted] Cleaning Procedure to Clean After Step", Document Ref: HQ.CLN.PL00290.4.PO, Version 4, Effective date: 6/21/13 was reviewed that describes how to clean the equipment train to include the mobile tanks, "TAM" containers, and how each piece of equipment is cleaned. The documentation is placed in the batch record.

Cleaning Validation

The following documentation regarding Cleaning Validation was reviewed:

- [redacted] -Cleaning Validation Plan", Document Ref: HQ.CLN.CVPL004.3 EN Version 3, Effective Date: 3/13/13
- [redacted] – Non Cleaning protocol including [redacted] Process 04, Document Ref: HQ.CLN.CVPL050.0EN, approved on 3/13/13

Previous Cleaning Validations conducted in 2010 were reviewed to include:

- [redacted] – Cleaning Validation Report, Document Ref: HQ.CLN.CVRP004.0EN, approved on 5/3/11"
- [redacted] – Cleaning Validation Plan, Document Ref HQ.CLN.CVPL004.2.EN, approved on 10/13/10
- [redacted] – Non-Cleaning Protocol, Document Ref: HQ.CLN.CVPR002.0.EN, approved on 6/1/10 was reviewed.

Cleaning Sanitizers

The following documentation was reviewed in regard to the sanitizers used:

- Written procedure entitled, "Cleaning and Sanitization of Clean Rooms – Annex A1 – Internal Operating Procedure", Document Ref : HQ.GQ.IOP.A1.0.EN approved on 7/2/03 was reviewed. This describes the preparation of sanitization agents that are used for surfaces.

Sanitization agents such as [redacted] are considered 'Agent B', which is diluted and used for the cleaning of the 100,000 clean rooms and are switched every 3 months. Cleaning includes the surfaces in the room including floor, exhaust system (grids), walls, doors, windows, airlocks, and ceilings. The diluted solution is valid for 7 days, however there is no supporting documentation to show this is expiration date is valid for the [redacted] from the supplier, NCH Portugal. ***Refer to Discussion with Management, Issue #2.***

- The Internal Operating Procedure entitled, "Cleaning and Sanitization of Controlled Rooms". Document Ref: HQ.GQIOP041.2.EN, Version 2, Effective Date 7/26/11 was reviewed.

- Room Logbook SLO707 documenting cleaning performed

- Microbiological report 70% Ethanol Challenge Test LEF Study No: PEI/2011/00925, REL 171/11 – Revision 0, May 2011, approved on 5/27/11 documents the neutralizer efficacy study, neutralizer validation, and stability of prepared disinfectant solutions.

MATERIALS SYSTEM

Purified Water System

The written procedure entitled, "Management and Maintenance Control of Purified Water System (SPA02, T650 and TA39)", Ref Document: HQ.HW.IOP032.5.PO, Version 5, approved on 1/15/13 was reviewed.

In addition, the firm writes a Purified Water monitoring report on an annual basis. The report entitled, "Purified Water – Trend Analysis of Results from B15/7Loop (January 2012 to December 2012)", Document Ref: HQ.QSR.MI079.0.EN, approved on 2/7/13 was reviewed with no issues observed. Information includes the evaluation of chemical and microbial results, and trending performed.

The sampling and microbial testing of Purified Water is performed by SMAS- Loures Laboratories. Chemical testing, description, and endotoxins determination is performed on-site.

Purified Water Qualification

There was a change on the Purified Water feeding line between UF system UF650 to include 3 new sampling points. In addition, sampling point SP60511was changed to stainless steel piping (from polypropylene). As a result, the P&ID drawings were updated and the PQ entitled, "Performance Requalification Report", Document Ref: HQ.QSR.EQ228.0.EN, approved on 6/29/12 was reviewed with no issues observed.

This PQ consisted of assessment of microbiological water's quality after the replacement of the polypropylene pipe to stainless steel during one month and against the specification in force (100cfu/ml). The 3 new sampling points (60514, 60515 and 60516) were monitored daily and tested for total counts on a daily basis and were tested on a weekly basis for endotoxins, on different days for each point. The data was reviewed with no issues observed.

PRODUCTION SYSTEM

Calculation and documentation of actual and theoretical yields

The calculation and documentation of actual and theoretical yields are documented on each batch record. For example, [redacted] Spray Dried Dispersion, Lot #HQ0020 was reviewed with no issues observed. In addition, the yield of each lot is reported on the Annual Product Review.

Batch Records

The batch record for [redacted] Spray Dried Dispersion, Lot [redacted].HQ00020 was reviewed with no issues observed.

Process Validation

The following documentation regarding Process Validation was reviewed:

- [redacted] - Process Validation Protocol", Document Ref No. HQ.QSP.PVP089.0EN", approved on 4/11/11
- [redacted] - Process Validation Report", Document No. HQ.QSR.PV118.0EN", approved on 9/22/11

Revalidation due to scale up include:

- [redacted] – Process Validation Protocol Scale Up", Document Ref: HQ.QSP.PVP117.1.EN", approved on 11/11/12
- [redacted] – Process Validation Report Scale Up", Document Ref: HQ.QSR.PV152.0.EN", approved on 3/29/13

Calibration/Maintenance

The following documentation was reviewed regarding calibration/maintenance:
In dispensing area:

- Scale BA12, annual calibrated on 9/12/13
- Scale BA156, annual calibration on 9/12/13
- Logbook BA12, HQ.QSD.RF853

- Logbook BA156, HQ.QSD.RF852

In Building 7 (where finished API is weighed):

- Scale BA159: annual calibration on 4/18/13

PACKAGING AND LABELING SYSTEM

The packaging of [redacted] Spray Dried Dispersion occurs in Building 7, in Room SL0707. The product is directly discharged into a PE bag that is ID tagged, a desiccant is added, then directly placed into an Aluminum bag that is sealed.

Copy of all label specimens

A copy of all labels are attached to the batch record. For example, [redacted] Spray Dried Dispersion, Lot #HQ0020 was reviewed with no issues observed

Reconciliation of labels

The reconciliation of labels are documented in each batch record. No issues were observed during the review of the batch record for [redacted] Spray Dried Dispersion, Lot #HQ0020.

LABORATORY CONTROL SYSTEM

Quality Control

Laboratory Equipment Qualification

Sonicator Qualification was reviewed to include:

- "UltraSonifier Bath – Branson 8800 Operational Verification Tests Report, approved on 9/6/13

- Operational Verification Test Report, Document HQ.QSR.EQ282

Reference Standards

During the walk through of the QC laboratory, the reference standards were reviewed. No issues were observed with the storage and identification of reference standards. In addition, if internal

reference standards are used, they are compared to the USP/EP. For example, the comparison data for the internal reference standard, Fluticasone, HQ000038 was reviewed with no issues observed.

Validation of Analytical Methods

Hovione validated all the analytical methods and also gave a copy to the customer as reference. The following analytical method validations were reviewed with no issues observed:

- Validation Protocol AVP-0134(1.0), "Qualification Protocol for the HPLC Method for the Assay and Impurity Analysis of [redacted] Drug Substance", approved May 18. 2009
- Validation Protocol AVP-0141(1.0), "Supplemental Validation Protocol for the Assay and Impurity Analysis of [redacted] Drug Substance at Hovione", approved June 25. 2009. This was written to add Robustness and Forced Degradation studies.
- CRLC3648 [redacted] "Assay and Related Substances (by HPLC) - Validation Report HQ.QSR.MV437.1.EN", approved on 7/16/11
- Validation Protocol for the HS-GC Residual - AVP-0056
- "Validation Protocol for the HS-GC Residual Solvent Method for [redacted] Drug Substance (revision)", AVP-0056, Effective Date: 9/22/08
- CRGC3320: [redacted]: "Determination of Residual Solvents in [redacted] (by GC-HS) Validation Protocol", Document Ref: HQ.QSR.MV356.1EN, approved on 7/16/11
- CRGC3320: [redacted]: "Determination of Residual Solvents in [redacted] (by GC-HS) Validation Report", Document Ref: HQ.QSR.MV356.1EN, approved on 7/16/11
- Validation Protocol AVP-0148: "Validation Protocol for the HPLC Method for the Identification, Assay and Impurity Analysis of [redacted] Spray Dried Dispersion [redacted] Effective Date: 10/5/09
- CRL:C3858 – "Validation of the HPLC Method for the Identification, Assay and Impurity Analysis of [redacted] approved on 7/19/11
- Validation Protocol for Residual Solvents Determination in [redacted] Spray Dried Dispersion [redacted] by Headspace GC", Effective Date: 9/16/10

- Validation Report – "VAL-0265 Validation Report for the Determination of Residual Solvents in [redacted] Spray Dried Dispersion [redacted] by Headspace GC", Effective date: 4/15/11

In addition, the following analytical methods were reviewed and compared with the method validation with no issues observed:

- Analytical Method [redacted] – "Determination of Residual Solvents in [redacted] (by GC-HS)", Document ref: HQ.CR.GC3320-HQ-IP1.5EN, Effective Date: 9/3/12

- Analytical Method – [redacted] "Identification, Assay and Purity Analysis SDD. [redacted] (by HPLC)", Document Ref: HQ.CR.LC3858-HQ-FP1.4. EN, approved on 5/24/13

Out of Specification (OOS)

The written procedure entitled, "OOS Investigation", Document Ref.HQ.CCO.COP015.5EP, Version 5, Effective Date: 7/3/12 was reviewed.

An OOS is considered as a deviation, thus a deviation report is filled out by the responsible person, then the actual investigation is documented on the OOS report. The target for completion is within 30 business days.

An OOS or OOT result will be reported from the Analyst to the Supervisor within the next shift (24 hour period). A lab investigation will be performed and documented on an OOS form. An OOS is considered a deviation and is also recorded in the CAPA database.

If lab error not is confirmed, then a Cross Functional Investigation is conducted to include Production and the sampling that was performed.

There were no OOS for [redacted] intermediates, API or the Spray Dried Dispersed (SDD) products.

The following OOS reports were reviewed:

Deviation ID 23431: [redacted]
OOS of major unspecified impurity at18M (2C-8C)
Occurred on 11/13/12 on 2 samples

Sample was prepared and loaded onto HPLC equipment, system suitability failed. Purge to the injector and restarted the run. Used the same original sample, and since sample was temperature

sensitive the OOS resulted. Retest was performed on a new sample (since temp sensitive) and passed. 2nd and 3rd replicate was performed and all passed spec.

Deviation ID 15040:
OOS of major unspecified impurity at 0M
Temp of 2-8C
Confirmed OOS, it was expected due to an R&D trial batch, due to the Product Code 06.

Deviation ID: 25277:
Lot OOS due to positive growth of Staphlococcus Aureus. The specification is "absence" of growth. This batch was rejected. An investigation was conducted, and the root cause could not be confirmed. However, the potential root cause could have been the operator during the preparation of the batch. CAPAs include: an installation of laminar air flow for execution of preparations such as charge/discharge/assistance from the oven, feeding/scrape from the micronizer/sifter will be installed.

Deviation ID 25636: Potassium Carbonate
Lot #100432.HQ00017 (raw material) was OOS for LOD. The retest date was due on the Potassium Carbonate, thus was re-analyzed. The probable root cause is that Potassium Carbone is absorbent over time due to the history of the product. There was no retest and the raw material was rejected. This is a lot that will be destroyed, and was located in the rejected section of the warehouse.

Stability testing

There are stability chambers for long term and accelerated use. They are located in Building 6 and is continuously monitored through a BMS system. Each stability chamber has a logbook that documents when the operator enters/exits the chamber and when taking samples.

Stability testing is performed at Hovione. The Spray Dried Dispersion, Lot #HQ00019 long term and accelerated stability data was reviewed with supporting documentation with no issues observed.

Certificate of Analysis

The Certificate of Analysis of Spray Dried Dispersion, Lot# HQ00033 was compared with raw data and analytical methods. No issues were observed.

Microbiology Laboratory

A walk through of the Microbiology Laboratory was performed where it was observed there is no identification of approved media versus media that is under quarantine and stored in the Refrigerator. In addition, there is no segregation between approved and quarantined media. ***Refer to Discussion with Management, Issue #1.***

Media (in house/pre-made)

Growth promotion testing is conducted on incoming media. The Centrimide Agar, Lot #67824 was reviewed, however could not be found in the logbook. ***Refer to Discussion with Management, Issue #4.***

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

There were no Inspectional Observations issued to the firm, however there was a Discussion with Management. *Refer to Discussion with Management section within this report.*

REFUSALS

There were no refusals encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

A Discussion with Management was held at the end of inspection with Mr. Guy Villax, CEO, the most responsible person, as well as other key personnel. A list of personnel is attached as (***Exhibit YH #9***).

Firm management explained that the issues listed below will be evaluated:

Issue #1: At the time of the walk through of the Microbiology department, there is no identification of approved media versus media that is under quarantine.

Corrective Action: Firm management acknowledged this issue.

Prior to the close out, Mrs. Baretto took a photo of the refrigerator that identified green stickers to show the approved media. In addition, the photo showed the segregation between the approved media and the media in quarantine.

Issue #2: The sanitization solution, Agent B is valid for 7 days, however there is no supporting documentation to show effectiveness for this period of time for [redacted] supplied by NCH Portugal.

Corrective Action: Firm management acknowledged this issue and will conduct an evaluation.

The written procedure entitled, "Cleaning and Sanitization of Clean Rooms – Annex A1 – Internal Operating Procedure", Document Ref : HQ.GQ.IOP.A1.0.EN approved on 7/2/03 describes the preparation of sanitization agents (Agent B) that is used for surfaces ***Exhibit YH #10***). In addition, the firm provided a copy of the Certificate from the supplier, NCH Portugal stating the Disinfectant of [redacted] at 1.4% is effective for seven days (***Exhibit YH#11***). However, there is no additional data, information, or report to support this expiration date.

Issue #3: In review of the Complaint #12982, there is no CAPA assigned regarding the installation of the oil free compressor that will be installed by the end of 2013. However, the meeting minutes between [redacted] and Hovione, dated 7/30/13, document this CAPA.

Corrective Action: Firm management acknowledged, and will evaluate this issue.

Complaint# 12982 is regarding the unidentified peaks found for the [redacted] API. The CAPA explains that the installation of the oil free compressor is going to be conducted, however there is no internal CAPA # assigned (***Exhibit YH #12***). In addition, a meeting between [redacted] and Hovione occurred on 7/30/13 which documented the meeting minutes. It states this CAPA will be performed by the end of 2013 (***Exhibit YH #13***).

Issue #4: Centrimide Agar Lot #67824 documenting growth promotion testing could not be found in the logbook.

Corrective Action: Firm management acknowledged this issue.

Mrs. Barreto explained there was a lot # error in the Culture Media and Solutions: Preparation, Pre-Incubation, and Growth Promotion logbook, page 91 and the growth promotion testing was actually performed. The Microbiologist mistakenly wrote Lot #67848. The error was corrected in the logbook (***Exhibit YH #14***). In addition, a memo was written in regard to the transcription error (***Exhibit YH #15***). Microbiologists involved were made aware of the mistake and this issue will be presented to the Microbiology Department during the TOP5 meeting as an alert situation.

Issue #5: The written procedure entitled, "SOP - Quality Management – Product Quality Review", Document Ref: HQ.CCO.COP006.1.EN, Version 1, Effective Date: 1/15/11 was reviewed, however there is no timeframe for completion.

Corrective Action: Firm management acknowledged this issue.

Mrs. Paulo explained the firm is revising this procedure and determining a timeframe of 3 months. However, this written procedure is considered a corporate document, thus must be approved by all sites.

A copy of the of the original written procedure "SOP - Quality Management – Product Quality Review", Document Ref: HQ.CCO.COP006.1.EN, Version 1, Effective Date: 1/15/11, was provided as ***Exhibit YH# 16***. CAPA report, ID 25843, issued on 3/15/13 identifies that a definition of a timeframe should be defined (***Exhibit YH #17***). In addition, Mrs. Paulo provided a draft procedure stating a PQR should be issued no later than 3 months (***Exhibit YH #18***).

ADDITIONAL INFORMATION

Logistics and Accommodations

Original hotel accommodations was at Radisson Blu, Lisboa, located at Av Marechal Craveiro Lopes 390 Lisbon Pt 1749009. However I (YH) moved hotels due to the room being too close to the airport and could constantly hear plane activities. In addition, the internet is not consistent. I (YH) transferred to the Hotel Real Palácio, located at Rua Tomás Riberiro, 1050-228 Lisbon, Portugal. The telephone is +351 21 319 9500 and fax is +351 21 319 9501. The hotel website is www.hoteisreal.com. This hotel was within per diem with the current exchange rate, and had internet available for free. The hotel does not have WiFi, however has an internet cable that can be borrowed. This hotel is close to the city center and was within walking distance to restaurants, convenience stores and shopping.

The firm provided transportation to/from the facility to the hotel on a daily basis.

SAMPLES COLLECTED

No samples were collected during this inspection.

VOLUNTARY CORRECTIONS

The following corrective actions were reviewed from the previous drug FDA inspection that was conducted by CSO D. Greco, Senior Policy Advisor, V. Shah, Ph.D., and CMC Quality Reviewer, B. Krtyka, Ph.D., from 4/26/11 – 4/29/11:

Issue #1: The Quality Agreement with [redacted] does not specify that Hovione would be notified for any changes during the process. Ms. Paulo stated the discussion item regarding the supplier agreement had already been corrected. This was observed by VS.

Corrective Action: This issue is considered corrected. The Quality Agreement with [redacted] was reviewed. The current approved agreement was signed on 6/14/13. Changes are described and defined as Major Impact Change, Moderate Impact Change, Minor Impact Change. In addition, Section 3.10 Change Control – documents the party responsible for the types of changes listed.

Issue #2: Dr. Shah indicated that although he had some reservation with the proposed sampling plan, it is a discussion item and not an observation. He stated he will bring forward their proposed sampling plan and justification for further discussion and a decision at center level within the Office of Compliance.

As a result, a Request for Information Letter from CDER/OMPQ dated 10/6/11 was sent to the site for further information (***Exhibit YH #19***). The firm sent a response regarding the issues on 10/21/11 (***Exhibit YH #20***). Mrs. Paola explained there was no correspondence from the FDA after this letter and attachments were sent. The firm received a copy of the FMD-145 letter from FDA on 11/4/11 (***Exhibit YH #21***).

Corrective Action: After the closure of the previous inspection, there was no formal FDA request to change the proposed sampling plan. Thus the firm continues with their practice.

EXHIBITS COLLECTED

YH-1: A list of all products manufactured at the site

YH-2: A list of DMF/VMF products

YH-3: A list of U.S marketed products shipped to the United States to include the material name, batch #, quantity, customer and address shipped to, and delivery date

YH-4: A copy of the organizational charts of Hovione FarmaCiencia SA to include the Hovione Group, QA Development, QA Technical Operations, and QC Production Area as ***Exhibit YH #4***.

YH-5: Initial FAR was reported to the [redacted] FDA District on 7/10/13

YH-6: A follow up FAR was submitted on 7/25/13

YH-7: A follow up FAR was submitted on 8/15/13

YH-8: A Final FAR was submitted on 9/23/13

YH-9: List of personnel

YH-10: Written procedure entitled, "Cleaning and Sanitization of Clean Rooms – Annex A1 – Internal Operating Procedure", Document Ref : HQ.GQ.IOP.A1.0.EN approved on 7/2/03

YH-11: Certificate from the supplier, NCH Portugal stating the Disinfectant of [redacted] at 1.4% is effective for seven days

YH-12: Complaint# 12982 documenting the CAPAs that are going to be performed

YH-13: The meeting minutes between [redacted] and Hovione dated 7/30/13

YH-14: Culture Media and Solutions: Preparation, Pre-Incubation, and Growth Promotion logbook

YH-15: Memo was written in regard to the transcription error of the Centrimide agar, Batch #67824

YH-16: Written procedure entitled, "SOP - Quality Management – Product Quality Review", Document Ref: HQ.CCO.COP006.1.EN, Version 1, Effective Date: 1/15/11

YH-17: CAPA report, ID 25843, issued on 3/15/13

YH-18: A draft procedure of the PQR stating the timeframe should be issued no later than 3 months

YH-19: A Request for Information Letter from CDER/OMPQ dated 10/6/11

YH-20: The firm sent a response regarding the issues on 10/21/11

YH-21: A copy of the FMD-145 letter from FDA on 11/4/11

ATTACHMENTS

N/A

Yumi J. Hiramine, Investigator