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SUMMARY

This inspection of an API manufacturer was conducted under Operation ID 63766 as part of Trip # 2018-005D. This inspection provides GMP coverage for commercial products. The inspection was conducted in accordance with CP7356.002F Active Pharmaceutical Ingredient Process Inspections. During this inspection profile class CSN (Minocycline Hydrochloride, Fluticasone Propionate, Doxycycline) and CRU (Betamethasone Acetate) drug substance were covered.

The previous inspection was a Pre-approval driven assignment and was conducted in March 2017 and classified as VAI. That inspection resulted in following 483 observations: inadequate corrective actions of deviations and inadequate mock recall procedure, deviation procedure is not clear and/or followed regarding determining if deviations have occurred before, documenting deviations open for more than 30 days, and guidance for CAPA effectiveness and trend handling. In addition, there were no operating procedures or preventative maintenance for a scale used in the manufacturing area and lack of identification of cleaned utensils used in the manufacturing area. Liquid Nitrogen distribution system is not qualified and routinely monitored and sampled. Employees engaged in the GMP environment have not received GMP

refresher training for more than two years, rejected materials were not placed in designated and restricted access area to prevent mix-up, 6) Gaps of various sizes on facility exit doors.

During this inspection, the corrective actions were verified.

The current inspection found that this site is still operating as drug substance manufacturer. This GMP inspection covered the Quality, Material, Laboratory, Production, facility and equipment systems. No deficiencies were noted and no FDA-483 was issued, however, one item was discussed during the close out meeting. The external lab used for analytical test is not identified in submitted DMF.

As per Director of Regulatory Affairs, the external lab used for Palladium and Rhodium content in final products and method validation for different tests, however this external lab is not identified in submitted DMF. Regulatory Affairs provided a commitment letter to update DMF.

EXHIBIT 01 Commitment to update DMF from Regulatory Affair

The firm was cooperative and made no refusals. No samples were collected.

ADMINISTRATIVE DATA

Inspected firm:	Hovione FarmaCiencia SA
Location:	Quinta S. Pedro, Sete Casas 2674 506 Loures, (Lisbon), 2674-506 Portugal
Phone:	351219829000
FAX:	351219829388
Mailing address:	Quinta S. Pedro, Sete Casas 2674 506 Loures, (Lisbon), 2674-506Portugal
Dates of inspection:	10/30/2017-10/31/2017, 11/2/2017-11/3/2017
Days in the facility:	4

Participants: **Parul M Patel, Investigator - Dedicated Drug Cadre**

Non-FDA Participants: None

On October 30, 2017, I presented my credential to Mr. Guy Vilax, Chief Executive Officer, who identified as the most responsible person at the site. He was present during opening and close out meeting. I explained the purpose of this inspection and then the management gave an introduction of managers. The Plant Manager provided presentation including history of the firm and Head of Quality Management provided presentation of the quality system.

Following individuals present during opening meeting:
Luisa Paulo, Corporate QA Director
Filipe Vicente, Plant General Manager
Joana Ferriea, Head of Quality Management System
Rita Mexia, QA Technical Expert
Roisin Hickey, QA Director of Cork site
Andreia Correaia, Quality Assurance Technician
Joao Alves, QA Director
Joerg Gam, Vice President of Quality unit

Regulatory communication should be address to:

Mr. Filipe Rosa Vicente, Site General Manager
Hovione FarmaCiencia SA
Quinta S. Pedro
Sete Casas 2674 506
Loures, Portugal
Phone 351 21 9829000
Fax 351 21 9829388
fvicente@hovione.com
or
Ms. Luisa Paulo, Corporate QA Director
Hovione FarmaCiencia SA
Campus do Lumiar, Edificio R
Estrada do Paço do Lumiar 1649-038 Lisboa, Portugal
Phone: 351219829172
Email: mlpaulo@hovione.com
Firm's website is www.hovione.com

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HISTORY

No significant changes since the previous inspection. The Hovione site continues to manufacture APIs via chemical synthesis (eg. Minocycline, Doxycycline) and processed salt (eg. Betamethasone Acetate) for the USA and other countries. In January 2017, the firm acquired warehouse for the storage of the raw materials and finished products. The new warehouse is located approximately 6 km from the airport and 12 km from this site.

There are 1,090 employees on site. The area of this site is 19,530 square meter and the consist of total 22 buildings. The annual sale in 2016 from this site was $164 Million.

The firm has a total of four manufacturing sites worldwide. two R&D sites and five administrative offices.

Corporate office located at: Hovione FarmaCiencia SACampus do Lumiar, Edificio R, Estrada do Paço do Lumiar,1649-038 Lisboa -Portugal

Production hours are 24/7, two or three shifts 8 and 12 hours.
Administration hours are from 8:00AM-6:00PM Monday through Friday.

The firm's registration with USFDA is current.

INTERSTATE (I.S.) COMMERCE/JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)

The firm manufactured drug substance for US market. As such, the firm is subject to the adulteration provisions of section 501(a)(2)(b) of the Act, which requires all drugs to be manufactured in accordance with the current Good Manufacturing Practices outlined in 21 CFR 210/211.

Approximately 65% of the Hovione Loures commercial products are shipped to the US market. Annual sales for the Loures site is approximately $164 million USD.

The firm currently manufactures and ships to the U.S market a total of twenty-seven products. Refer to list of products and customers in the US Exhibit

The firm manufactures and ships commercial APIs to the U.S market

EXHIBIT 02 List of US products manufactured at this site

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Mr. Guy Villax, CEO. is responsible for defining the overall company strategy and providing enough resources to the sites. He is the most responsible person at the site.

Luis Gomes, Vice President Manufacturing, is responsible for managing all sites to ensure that necessary resources are available to implement company strategy and achieve company objectives with high standards of product quality and health safety and environment. He reports directly to Mr. Villax.

Mr. Filipe Rosa Vicente, Site Manager, is responsible for managing all activities of this site and staff to achieve high standards of product quality to comply with production plans, to maintain and improve the financial aspects of operations. and to guarantee that safety is observed everywhere; allocates funds towards GMP corrections. He reports to directly Mr. Gomes.

Ms. Luisa Paulo, Compliance Director, is responsible for assuring that all approved procedures follow the applicable regulations, that they are necessary for the development of Hovione' s business and they are in line with the company strategic plan and policies and assures the implementation of procedures developed and established by the Corporate QA areas. She reports to Mr. Villax.

Mr. David Martins, Production Director, Pharmaceutical Operations, is responsible for assuring the achievement of internal production targets, by devising, developing and establishing effective production strategies and efficient working practices, and by devising the tactics for the concretization of Hovione global strategy. He reports to Mr. Vicente.

Mr. Pedro Duarte, Production Director. Chemical Operations, is responsible for assuring the maximum level of customer satisfaction and establishing the conditions for the recognition of the company by its customers as being trustful, reliable and innovative, with the technical. organizational and motivational abilities that differentiate it from the competition, allocates funds towards GMP corrections, and has hire and fire authority. He reports to Mr. Vicente.

Mr. Jose Lisboa, QA Manufacturing Director, is responsible for the development and implementation of the Quality System to support the manufacturing activities; to develop and propose in collaboration with other QA members. the establishment of the best quality practices to make the different through creative, simplified, and innovative procedures. He also promotes and establishes the objectives for all areas under his responsibility per the strategy of the company and allowing a cascade between all levels. He has the authority to hire and fire.

Ilda Chasqueira, Head of QA Drug Products, is responsible for product quality and to protect the interests of customers and patients, works autonomously and accountably to direct reports, clients and regulators. His job function should assure compliance of all applicable quality guidelines and regulations, coach and promote autonomy, training, development of all QA members, supporting rotations programs, and enabling optimal career progression of QA members.

Mr. Manuel Carvalho, Head of Warehouse, is responsible for all warehouse activities, ensures the Quality Policy is followed, ensures Logistics GMP/GDP compliance, prepares the yearly training program and identifies the necessity of training and optimize resources and procedures for continues improvement. He reports to Logistics Director.

EXHIBIT 05 Organization chart
EXHIBIT 06 Firm's presentation

FIRM'S TRAINING PROGRAM

All employee training is managed as per written procedure COP 007 titled "Training." GMP refresher training is provided yearly since June as a corrective action of the previous observation. During this inspection, I reviewed the training procedure and training records of QA and production personnel. The training records are maintained in "Train Stream" software. Relevant section head is responsible for their employee training. Whenever any procedure or instruction is updated, an employee dashboard is updated. Training evaluation may include the written test.

As per corporate QA Manager, the "Train Stream" software will be replaced with new software "Corner Stone" in the end of the 2017. The software validation was ongoing during inspection.

MANUFACTURING/DESIGN OPERATIONS

Quality manual describes the quality management system. Site quality assurance is responsible for the evaluation of all quality matters related with site quality system and products under development and commercial as applicable to the site. Corporate quality is responsible for the quality and HSE system of Hovione group including validation, qualification, and data integrity. All commercial batches are released by the Qualifies Person and QA issues the Certificate of Analysis electronically from LIMS system. The Qualified Person and QA ensure that the necessary and relevant tests for the commercial batch are carried out and fulfill the requirement, and were manufactured as per established validated procedure and GMPs. QA reviews all batch related documents prior to release.
Quality unit is responsible to assure that all approved procedures are followed, review all GMP documents, prepare annual product review, manage quality related deviation, change control, OOS investigation, rejects, returns, recall, complaints, and communicate with customers and regulatory agencies as necessary. QA also manage suppliers and contractors. There is a total of 92 employees in Quality Unit.

The quality documents are managed by different modules, DocStream for document control, ChangeSteam for change control, CAPA, and deviation, TrainStream for and training. The Training module will be updated in Dec 2017 after completion of validation.

Deviation
The new updated deviation management procedure includes to trend deviations and monitor corrective actions.
Deviations are managed as per procedure COP.014 "Deviation Procedure." During inspection, I requested list of deviations since last inspection. I reviewed the deviation procedure and randomly selected deviations in detail from list.

Deviation [redacted] was opened for an Out of limit drying temperature during Fluticasone Propionate batch [redacted] The root cause was detected that brine flow in the cooling system was interrupted and temperature was not reduced within time. The corrective action was to repair leaking pipe. I verified that implemented corrective action is effective and the batches manufactured as per validated process.

Out of Specification
Out-of-specification results are managed as per procedure HQ.CCO.CO.15 "OOS investigation." During inspection, I requested list of OOS since last inspection and reviewed randomly selected OOS investigation in detail.

OOS investigation no. [redacted] related to water content failure during 6M and 9M stability of Minocycline Hydrochloride batch [redacted] was reviewed. Laboratory repeated the test from the original sample and new sample of the same batch. The results of both samples met specification. No laboratory error detected. The stability samples were packaged by the QC analyst from bulk sample. The root cause was detected that packaging of stability sample was performed in uncontrolled room (in QC laboratory and was not monitored for humidity) and may cause OOS water content result. The corrective action includes packaging of stability, retain, and release sample by the production operators during final packaging in the controlled room in manufacturing area. I verified the corrective action in packaging records for Minocycline Hydrochloride batch [redacted] under CAPA [redacted]

OOS investigation [redacted] related to higher Methanol content in [redacted] intermediate batch no. [redacted]. No lab error detected and OOS result was confirmed. I reviewed the audit trail of the analytical data. The corrective action was to repeat drying step of the intermediate batch. Analytical data of the dried batch met established specification and was released for further process.

OOS investigation [redacted] related to microbial contamination in Fluticasone Propionate inhalation grade [redacted] During microbiological analysis *Staphylococcus aureus* and *Stenotrophomonas maltophilia* growth was detected and the batch was rejected. No laboratory error detected, production investigation includes the sanitization of the equipment, filter integrity, status of sampling tool, and raw material quality.
The probable root cause detected that the contamination may be due to an environment condition in

the production area or by the operator. The packaging activity was performed inside clean room Grade D (SEMB0101) in building 1. The corrective action is to perform packaging activity in the cleanroom Grade D (SLO703) inside disposable glove bag (gamma radiated) in the building 7.
The rejected batch was reprocessed and the reprocess batch [redacted] met established specification and was release for commercial.

Minocycline Hydrochloride batch no [redacted] was rejected due to OOS result of particle size distribution of 91% with IPC specification <95%. The event was raised and root cause was detected as malfunction of the double cone drier vacuum system SB2501. The vacuum system was dismantled and detected that air retrieve injector and condensate purge was clogged. The air retrieve injector and condensate purge was changed. Previous and ongoing batches were evaluated and there was no quality impact on batches. The annual maintenance of the drier was performed by a contractor and verified the condensate purge. In addition, new maintenance employee was hired to ensure that the contractor follows the established procedures.
The batch was rejected and reprocessed into a new batch [redacted] The reprocess steps were validated and previous reprocess batch was included into stability. The stability summary of Minocycline Hydrochloride batch [redacted] was reviewed and no deficiencies noted.
The reprocess of batch is processed as per approved procedure HE-CCO-COP028 titled "Reprocessing, reworking, and returned product."

There are no returns since previous inspection.

MATERIAL SYSTEM:

All starting materials and packaging material are purchased only from approved vendors. Vendor qualification is performed by QA as per written procedure no. HQ.CO.SOP105.6 titled "Supplier Qualification." Vendor qualification of starting material includes site audit (every three years), declaration of TSE, BSE, process impurities, and verify vendor's test results. Reduced testing may be implemented to the material received from qualified vendor and QA approval through change control. No vendor change since previous inspection. Rejected non-conforming material is segregated in rejected area of the warehouse. Only quality assurance can handle rejected products. Purchasing department informs supplier and it can be returned to supplier or destroyed.

Incoming material is inspected upon receipt, tested to determine its conformance to established specification. Status of material is controlled by SAP system, no extra labeling is performed. Primary packaging LDPE bag are analyzed for description, identification, differential scanning colorimetry, nonvolatile residue, residue on ignition, and heavy metals. LDPE bag are sent for Gamma radiation and analyzed for ID and microbial evaluation by contact plate. These bags are used for Betamethasone and Fluticasone Propionate.

Nitrogen gas is used for spray drier. The monitoring for the Nitrogen distribution system includes, annually monitoring distribution loop for purity, appearance, Oxygen, Carbon dioxide, carbon monoxide, water content, Sulfur dioxide, Nitrogen Oxide, and microbial contamination. The chemical analysis for Nitrogen is performed by the external laboratories, Tradelabor Laboratory and TraceAnalytics laboratory. The usage point of use had 0.2-micron nitrogen absolute filter.

The liquid nitrogen is converted into a gas and distributed to each point of use (POU). At each POU, the nitrogen gas is filtered using a 0.2µm filter replaced annually and integrity tested every 6 months. Filtered nitrogen is used in Building 15 for different steps in the [redacted] process including the S901 dryer with direct contact during the [redacted] drying step.

EXHIBIT 04 Validation report of Nitrogen distribution supply

Purified water
There is no change in water system since last inspection. Purified water is used for production and equipment cleaning. Purified water system is monitored by procedure HQ.DQ.SOP 099.9 titled "Management, Control and Maintenance of the Quality of Water." During inspection, I reviewed purified water trend data from October 2016 to September 2017 including OOS investigation OOS [redacted] related Purified water usage point PU19 above specification limit for total microbial.

FACILITY AND EQUIPMENT SYSTEM:

There are total of twenty buildings at this site. The land area is approximately 42,500 square meters. All buildings are constructed in concrete base. The building 13a, 13b, part of 4 and 2 are dedicated for tetracycline products. Building 1 is dedicated to Corticosteroids products, building 8 is for raw material and intermediate storage, and building 9 is a pilot plant. I performed inspectional walkthrough of the facility. The facility appears to be spacious and maintained with qualified equipment. There is no new equipment since last inspection.

As per QA manager, in near future, new building will be used for administrative, canteen, and centralize QC laboratory.
The pest control is managed by QA and performed by a contractor, Rentokil Pest Control. The pest control activities are performed as per firm's procedure HQ.DQ.SOP 059.12 titled "Pest Control." The recent pest control report was reviewed

Final packaging activities are performed in the controlled room. Packaging room is monitored for temperature (<25°C), humidity (40-70%), and positive pressure.

Equipment cleaning verification and validation are described in SOP HQ.CCO.COP026.9 EN titled "Cleaning Verification and Validation." The procedure outlines the risk based cleaning assessment, use of cleaning agents, cleaning procedures in detail, dirty hold time, verification and acceptance criteria.
The new product [redacted] process was introduced in 2013. Cleaning of glass lined reactor R302, spray drier SD1251, and double cone-drier S901 were evaluated before validation batches. The equipment cleaning risk assessment includes solubility, established acceptance criteria based on daily dose, toxicology, cleaning agent, and recovery rate.

Cleaning verification within campaign includes visual inspection and cleaning verification sample with <300ppm product carryover.
Cleaning verification sample with <100ppm product carryover whenever there is product changeover.

Cleaning verification sample with <10ppm carryover which is applicable to drug product for clinical and there is non-chemical reaction of API (blending, micronization).

Preventive maintenance of Spray Drier 1251 in SAP was reviewed. The spark test of glass lined reactors are performed yearly and was reviewed. HEPA filter of spray drier is replaced after each product campaign.

EXHIBIT 06 Facility layout- page 19 of 35

PRODUCTION SYSTEM:

This site manufactures non-sterile drug substances and intermediates for clinical trial or commercial. B-lactams and Penicillin are not manufactured at this site. All products are produced in multipurpose equipment. Master Batch Record is approved by QA. Batch record printed by production engineer, batch number generated by SAP is stamped in blue, issued verified by second person, executed to operator, after completion of batch production the executed BMR is reviewed by engineer, and final review by QA with analytical data and data from Delta-V (DCR software) records.

Batch record review includes review of all process parameters, in-process data, yield, material used, reconciliation, LIMS results, process and analytical deviations, CAPA, cleaning verification records, and change control. Qualified person authorized the release of the batch for commercial and QA approves the COA prior to ship batch.

BMR of Minocycline Hydrochloride batch [redacted] and Betamethasone 21-acetate batch [redacted] were reviewed.

Batch is released by Qualified Person as per approved procedure DQ. SOP.183 titled "Batch Release."

Online monitoring system DELTA –V records and control the reaction temperature, charging of solvent, charging gas, measure pH, and pressure.

LABORAOTRY SYSTEM:

The quality control laboratory is responsible for testing and approval of raw materials, testing of vendor qualification samples, cleaning verification, water analysis, evaluate environmental monitoring samples, in-process samples, stability and final product. In addition, microbial test method validation, analyst qualification, manage retain samples, maintain and qualify analytical standard, performance qualification of analytical instrument, deviation investigation (OOS, OOT), review analytical data.
All analytical data is recorded in LIMS Systems by the analyst who performed the test and reviewed by the QC supervisor. Analytical data is also recorded in analyst log-book or equipment log-book. Analytical instrument calibration and qualification is performed by maintenance department as per established plan in SAP.

Retain sample is collected by production operator during final packaging of finished product and stored in building 22.
Chromatography instrument software for GC and HPLC is Empower-3. During inspection, I verified the analyst, reviewer, and laboratory administration role for Empower software. Audit trail was reviewed during inspection and no abnormality detected.

Analytical data review includes the review of chromatographic analysis, audit trail, instrument logbook, method used, system suitability, verification data in LIMS, reference standard used, calibration status of analytical instrument, and regents used for the analysis.

PACKAGINING AND LABELING:

Production department request the generation of label into SAP and prints after QA approval, prior to ship the warehouse label is replaced with the shipping label (original label kept in shipping document). Second warehouse personnel verify the product label prior to ship.
Reconciliation of printed labels is documented into the batch manufacturing record and was verified during inspection.

MANUFACTURING CODES

The batch number is assigned through SAP software as per procedure no. COP041.3 titled "Material Codification."
Final API batch number is containing product code followed by sequential batch number. For example:

05NY01.HQ01081 where 05 represents material group, NY01 represents material code, HQ is manufacturing site code, 01081 is the sequential number of the material.

The finished product material code 05 is for generic products, 17 is for contract manufactured products, 19 for bulk intermediate, and 20 for drug product (for clinical).

COMPLAINTS

All complaints are managed as per established procedure. Complaint is logged by the receiver and informed to the quality manager. The relevant area will start the investigation to detect root cause and implement corrective action. if needed.

RECALL PROCEDURES

Market recall is managed as per written procedure HQ.CCO.COP030.2 titled "Recall." Frim had no recall since last inspection. As per approved procedure the yearly mock recall was performed and reviewed during this inspection. Recall will be communicated within 15 days to the regulatory

agencies with corrective action.

REFUSALS

No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT

On November 3. 2017. I held a close out meeting with following firm's management.
Guy Villax, CEO
Filpe Rosa Vincente, Site Manager
Luisa Paulo, Corporate Quality Senior Director
David Martins, Pharmaceutical Operation Director
Pedro Duarte, Chemical Operation Director
Jose Lisboa, Quality Performance Director
Joao Alves, Site Quality Director
Cristina Alves, Quality Control Director
Manuel Carvalho, Warehouse Head
Joerg Gampfer, VP Quality
Roisin Hickey, Quality Assurance Director from Ireland site
Rita Mexia, Quality Assurance Technical Expert
Joana Ferreira, Head of Quality System Management
Hugo Galaio, Logistics Director
Sonia Amral, Head of Analytical Expansion

During close out meeting, I informed firm's management that it is the firm's responsibility to evaluate all their system to determine compliance with cGMP regulations. One item was discussed with management. The external lab used for finished product test was not included in submitted DMF. Regulatory Affair manager provided a commitment letter to update DMF. See Exhibit 01.

SAMPLES COLLECTED

No sample collected during this inspection

VOLUNTARY CORRECTIONS

Correction of previous FDA 483 observations were verified. During this inspection one discussion item was discussed during the close out meeting. The external lab used for analytical test is not identified in submitted DMF.
As per Director of Regulatory Affairs, the external lab used for Palladium and Rhodium content in final products and method validation for different tests, however this external lab is not identified in submitted DMF. Regulatory Affairs provided a commitment letter to update DMF.

EXHIBIT 01 Commitment to update DMF from Regulatory Affair

EXHIBITS COLLECTED

1 Exhibit 1 Commitment to update DMF from Regulatory Affair, 5 pages
2 Exhibit 2, List of US products 3 pages
3 Exhibit 3, List of US shipped batches, 15 pages
4 Exhibit 4, Nitrogen validation report, 11 pages
5 Exhibit 5, Organization chart, 6 pages
6 Exhibit 6, Firm's presentation, 31 pages

ATTACHMENTS

1 IFR, 2 page

X Parul M. Patel -S

Digitally signed by Parul M. Patel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Parul M. Patel -S, 0.9.2342.19200300.100.1.1=1300089255
Date: 2018.01.16 09:15:54 -05'00'