DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Surveillance
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08/15/2016

Hovione PharmaScience Limited
Estrada Coronel Nicolau de Mesquita S/N
Taipa, , MO

Reference: Inspection Date(s): 05/16/2016 - 05/20/2016

Location: Hovione PharmaScience Limited
Estrada Coronel Niclau Mesquita
Taipa, , MO

Dear Mr. Eddy Leong,

We are enclosing a copy of the establishment inspection report (EIR) for the inspection that the U.S. Food and Drug Administration (FDA) conducted at your premises on the referenced locale and date(s). When the Agency concludes that an inspection is "closed" under 21 CFR 20.64(d)(3), it will release a copy of the EIR to the inspected establishment. This procedure is applicable to EIRs for inspections completed on or after April 1, 1997.

The Agency continually works 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 Freedom of Information Act (FOIA) and 21 CFR Part 20. This, however, does not preclude you from requesting additional information under FOIA.

If there is any question about the released information, feel free to contact me at 240-402-6594.

For more information on the U.S. FDA, please visit our website at www.fda.gov.

Sincerely,

Jeneen Hatch
for.
Coki Cruz

FEI: 3002807210

Enclosure: Establishment Inspection Report (EIR)

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SUMMARY

This was a pre-announced routine GMP and Pre-Approval inspection of an Active Pharmaceutical Ingredients (API) manufacturer called Hovione Pharma Science located in Macau. This inspection was conducted by request from ORA/Division of Medical Products and Tobacco Inspections (DMPTI), Trip No: 2016-227D, and FACTS assignment ID# 11620460. This inspection was conducted in accordance to Compliance Program CP 7356.002F - Active Pharmaceutical Ingredient (API) Process Inspection (PAC# 56002F), CP7371.001 Animal Drug Manufacturing Inspections (PAC# 71001B) and CP 7346.832 Pre-Approval Inspections (PAC# 52832). ICH Q7A was also used as a guide. This was a comprehensive inspection covering Quality, Materials, Production, and Laboratory. Limited coverage of Facilities & Equipment and Labeling & Packaging systems were performed. The firm's profile class CSN (Non-Sterile Chemical Synthesis) was covered during this inspection.

The previous inspection was conducted in January 2013 and was classified as NAI. No Form

FDA-483 was issued.

The current inspection revealed the firm continues to manufacture Human and Veterinary API products for domestic market (China) as well as international markets (including Europe and United States). Currently, the firm manufactures four API products for US market (Doxycycline Hyclate & micronized form), Doxycyline Monohydrate (& micronized form), Ivermectin, and [redacted]. This comprehensive GMP inspection covered Quality, Materials, Production, Laboratory, Facilities & Equipment, and Packaging & Labeling as well as the pre-approval for Doxycyline Monohydrate (micronized).

There were no major objectionable conditions observed at the firm during this inspection and no FDA-483 was issued at the closeout meeting. No samples were collected and no refusals were received during the inspection.

ADMINISTRATIVE DATA

Inspected firm:	Hovione PharmaScience Limited
Location:	Estrada Coronel Nicolau de Mesquita Taipa, Macau SAR
Phone:	(8532) 882-7544
FAX:	(8532) 882-7714
Mailing address:	Estrada Coronel Nicolau de Mesquita Taipa, Macau SAR
Dates of inspection:	05/16 20/2016
Days in the facility:	5
Participants:	Stacie A. Woods, Investigator Truong (Andy) Nguyen, Investigator

Official credentials were presented to Mr. Eddy Leong, General Manager, at the start of the inspection on Monday May 9, 2016. Mr. Eddy Leong stated that he was the most responsible person at the firm.

There were no other government agencies present at the firm during this inspection. Mr. José Lisboa, Corporate QA Director, who represents the corporate office located in Portugal was present during our inspection.

All sections in this EIR (Establishment Inspection Report) were written by Investigator Truong Xuan Nguyen (TXN) and Stacie A. Woods (SAW).

HISTORY (SAW)

Hovione Macau (HM) site was inspected initially by FDA in 1987. It has since been inspected on six other occasions (1991, 1996, 2000, 2004, 2009, and 2013). All inspections have been satisfactory and the firm has been found an acceptable supplier of the APIs.

The firm is also inspected routinely by the Local Health Authority and EU Health Authority.

Hovione, a privately held company was founded in Portugal in 1959 and has several offices around the world including five manufacturing facilities. The five manufacturing facilities are located in New Jersey, Ireland, Portugal, China, and Macau. Office locations include: Switzerland, Hong Kong, and India. Hovione registered the Macau site in 1984 and began operations in 1986. Hovione headquarters' address is: Hovione FarmaScience SA, Sete Casas, Loures, Portugal, 2674-506 (FEI#3002807208).

Hovione is an international group dedicated to the development and manufacture of APIs for the pharmaceutical industry. Their customers include biotechs, specialty, medium, large, and generic pharma. Hovione Macau location produces both generic and custom synthesis products.

Hovione Macau is located in a residential area and about 8 miles from the local Macau Airport. The Macau plant was built in 1986 and a major expansion was finished in 2001. The plant occupies a land area of approximately 11,000 m². The facility includes administration offices, QC laboratories, production buildings, warehouse facilities, and utility areas, covering a total area of approximately 6,000 m².

Hovione Macau site has approximately 162 employees and produces DMF and VMF products as explained below.

Product Name	Years Produced by Firm	DMF or VMF Numbers	Indicated For
Doxycycline Hyclate	29	DMF 13714	An antibiotic used to treat bacterial infections including those that cause acne, treats certain skin condition like rosacea.
Doxycycline Monohydrate	26	DMF 13710	An antibiotic used to treat bacterial infections. It works by slowing the growth of bacteria.
Doxycycline Monohydrate (Micronized)	8	DMF 23638	An antibiotic used to treat bacterial infections. It works by slowing the growth of bacteria.
Ivermectin	19	DMF 21395, sold to [redacted] to US	A broad-spectrum antiparasitic. Used in humans in the treatment for example of onchocerciasis.

[redacted]	17	VMF [redacted], held by the buyer.	Veterinary, treatment for equine protozoal myeloencephalitis

HM sales volume in fiscal year 2015 was 142 tons of all product combined. Sales to North America represented about 20% (US and Canada) and Europe 55% and the rest to Australia/New Zealand/Asia countries/Middle East/Africa.

The firm is registered with FDA. The firm is in operation 24 hours a day, seven days a week for production and QC. Production slows down during August and Chinese New Year. Plant maintenance shutdown is performed for 3 to 4 weeks in August.

A list of U.S. consignees is provided in **Exhibit SAW – 1**

All FDA correspondence and copy of the FMD 145 of this report should be addressed to:

Hovione PharmaScience Limited
Attn: Mr. Eddy Leong, General Manager
Estrada Coronel Nicolau de Mesquita
Taipa, Macau SAR

INTERSTATE COMMERCE / JURISDICTION (SAW)

The Hovione Macau plant produces APIs that are exported and marketed in the USA. **Exhibit SAW-2** is a complete list of lots and quantities shipped to the USA for use in connection with USA filed ANDA applications. Consequently, these actives produced by the Macau plant and exported to the USA are considered drugs by definition in the FD&C Act.

The following chart shows what the total quantity of each group of product produced at the firm and the quantity shipped to the US market. The bolded Material numbers are the products shipped to US.

Product	Material Code	Total Quantity produced (kg)	Total Quantity Shipped to US (kg)
Doxycycline Hyclate Micronized Milled	**05MA51U** 05MA51M 05MA51V	89,307.26	13,326.13
Doxycycline Monohydrate Micronized Milled	**05MA64U** **05MA64M** 05MA64V	48,775.50	7,422.33
Ivermectin	**05KB21**	602.61	140.60

	[redacted]	2,710.22	
[redacted]	[redacted]	2,811.94	2,809.98

[redacted] is an API for an animal drug. Doxycycline Hyclate, Doxycycline Monohydrate, and Ivermectin are APIs for human drugs.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED (SAW)

The following individuals were present during our inspection and provided information for this report. An HM Organizational Chart is provided in **Exhibit SAW-3.**

Mr. Eddy Leong - At the Onset of the inspection, we displayed our official credentials to Mr. Eddy Leong, General Manager. Mr. Eddy Leong is the site General Manager and the most responsible for company operations in Macau. He was present for the opening of inspection and for the closeout meeting and was onsite during our inspection dates. He has been employed at Hovione since 1997. He reports to the VP of Manufacturing. His job responsibilities include:

- Assessment and maintenance of suitable infrastructure, equipment, staff and work environment for the manufacturer of company products.
- Company development in training and maintenance of records.
- Promotes awareness of customer requirements and statutory, regulatory and legal requests.
- Business performance evaluation.
- Periodic reviews of the Quality Management System and the Environmental Management System.

Mr. Jose Libosa - Director QA Manufacturing. Mr. Libosa sits at the Head Quarters location in Portugal. He was present each day of our inspection. He has been employed at Hovione since 1983. He reports to the VP of Manufacturing. His job responsibilities include:

- Oversight of all QA organization sites under his responsibility to assure that all applicable procedures, established objectives and approved financial budgets are followed and achieved.
- Implementation of plans and rules established by Corporate Management.
- To establish with other Corporate Quality/Compliance Directors and VP Manufacturing milestones and key performance indicators to allow analysis and evaluation of results for a continuous improvement of the Quality System.

Ms. Rainbow Chung Head of QA. She was our primary contact person during our inspection. She was present each day during our inspection. She has been employed since 2002 and reports to the Director of QA Manufacturing. Her job responsibilities include:

- Assuring that cGMP compliance and ISO 9001 are implemented and maintained in manufacturing activities at Hovione Macau (HM).
- Managing the Quality Assurance Department's performance and contributing to its continuous improvement (QA KPI's).
- Promoting the importance of high quality levels and the importance of a continuous improvement culture in all core company activities.
- Align and harmonize the quality system procedures within HM and among all sites.
- Coordinate and coach QA and other operational area members.

Mr. Nelson Lio Head of QC. He has been employed at Hovione since 2006, and reports to Mr. Eddy Leong. His daily job responsibilities include:

- Guarantee of fulfilment of all cGMP requirements of the area as well as the Safety, Environmental and Health Regulations.
- Coordinates and assures objectives and harmonization is met in the QC laboratory.
- Supervises the QC Laboratory.
- Ensures the QC staff is trained.
- Ensures the inter- and intra- flow of information.
- Assures that the correct analytical support is given in time to internal and external customers by planning the work to be carried out in agreement with order processing.
- Assures the qualification, calibration, preventive and corrective maintenance and good functioning of the analytical equipment.

Mr. Johnny Cheong - Production Director. He has been employed at Hovione since 2006. He reports to Mr. Eddy Leong. His job responsibilities include:

- Accomplish the sales strategies and planning defined by the company by fulfilment of customers' orders according with agreed schedule, minimizing the respective costs via improved process yields and an efficient management of the operations.
- Study and implement new production lines projected to be run at Hovione.

Mr. Bowie Soe Head of Production. He was been employed by Hovione since 1996. He reports to the Production Director. His job responsibilities include:

- Manage the Production Department to achieve objectives.
- Ensure the execution of the Production Plan and the annual plan of Production department.
- Supervise the working conditions of the installations and equipment.

Mr. Daniel Mok Head of Industrial Engineering. He has been employed since 2000. He reports to Mr. Eddy Leong. His job responsibilities include:

- To provide the necessary support to maintain the functionality of all production and utilities equipment.
- To work towards the global technical direction established by HQ Engineering.
- To provide a reliable network in engineering related works including installation and maintenance work for HM users.
- To maintain the effectiveness of utilities equipment.

FIRM'S TRAINING PROGRAM (SAW)

I reviewed the Corporate Operating procedure, entitled Training, HQ.CCO.COP007.5.EP, effective 16 Feb 2016. They use TrainStream software to manage training courses and to document employee attendance.

Routine training is provided annually based on a written plan. Each department is responsible for developing a training plan for their department employees and to ensure that the employees under their area of responsibility is prepared, trained and qualified to perform job duties. GMP and safety training is given annually. Training consists of an evaluation to assess the effectiveness such as a paper test, e-test, or practical demonstration. QA (Mrs. Chung) is responsible for reviewing the training plan and assuring employees continued to receive adequate training. Some of the training is provided by Hovione's corporate through video conferencing.

Training records were satisfactory and no deficiencies were noted.

DRUG MASTER FILE (DMF 23638) FOR DOXYCYCLINE MONOHYDRATE MICRONIZED (TXN)

The original Drug Master File #23638 was submitted to the FDA on March 2010. Since 2010, there have been several amendments submitted to the FDA related to Manufacture, Control of Drug Substance, and Reference Standards. I reviewed the current and most updated Drug Master File 23638 related to Doxycycline Monohydrate, dated June 2012, Version 0001. According to the firm's management, they have submitted all of the amendments to the FDA including the most recent Annual Report on March 23, 2016.

I reviewed the following items related to the Drug Master File (DMF 23638):

- General Information (Nomenclature, Structure, and General Properties)
- Manufacture (Description of Manufacturing Process Controls, Control of Materials, Controls of Critical Steps and Intermediates, Process Validation & Evaluation)
- Characterization (Elucidation of Structure and Other Characteristics, Impurities)
- Control of Drug Substance (Specifications, Analytical Procedures for Triethylamine, Residual Solvents, Particle Size, Bulk & Tapped Density, Light Absorbing Impurities, Validation of Analytical Procedures, Batch Analysis, and Justification of Specification)
- Reference Standard and Materials (Drug Substance & Materials)
- Container Closure System (Primary Container: Polyethylene Bags; Secondary Container: Aluminum Laminated Bags; Export Container: Plastic Drum; Export Label).
- Stability (Stability Summary and Conclusions, Stability Protocol and Commitment, Stability Data)

According to Mrs. Chung, Head of Quality Assurance, there have been no changes to the manufacturing process, testing, and specification related to DMF 23638 beside those that have already been reported to the FDA.

PRE-APPROVAL FOR DOXYCYCLINE MONOHYDRATE MICRONIZED (DMF 23638 & [redacted]) (TXN)

Doxycycline Monohydrate micronized (DMF 23638) is referenced in [redacted]. Doxycycline Monohydrate micronized (Hovione's Internal Product Code: 05MA64M) is manufactured from Doxycycline Monohydrate, DMF 13710 (Hovione's Internal Product Code: 05MA64U) drug substance. The firm has been making Doxycycline Monohydrate API (DMF 13710) for over 26 years and Doxycycline Monohydrate micronized form (DMF 23638), product code: 05MA64M for about 8 years.

The manufacturing process used by Hovione to micronize Doxycycline Monohydrate (DMF 23638) consists only on a physical process to reduce the particle size through a fluid energy Jet Mill (micronizer), which does not involve chemical transformations of drug substance, neither the addition of solvents nor other raw materials. The chemical synthesis and manufacturing process for Doxycycline Monohydrate is fully described in the Drug Master File Type II, No. 13710, submitted to Food and Drug Administration by Hovione (DMF holder Hovione FarmaCiencia SA).

OBJECTIVES FOR PRE-APPROVAL (TXN)

1. Is the firm ready for commercial manufacturing of this product? Yes. The firm has been producing Doxycycline Monohydrate for the past 26 years and Doxycycline Monohydrate micronized form for the past 8 years. Please refer to the rest of the EIR for more information.
2. Is the firm confirming to application? Yes, the firm is producing the Doxycycline Monohydrate micronized according to DMF 23638.
3. Did data integrity audit yield acceptable findings? Yes, the review of test records and production batch records yield acceptable findings.

MANUFACTURING/DESIGN OPERATIONS (SAW & TXN)

QUALITY SYSTEM (SAW)

Annual Product Review

The APR SOP requires the review to be done annually. The reporting period covers production from April to March. I reviewed procedure entitled Product Quality Review, HQ.CCO.COP006.2.EN, and effective date 23 Oct 2014.

I reviewed the APR for Doxycycline Hydrate, Doxycycline Monohydrate, and Doxycycline Monohydrate (micronized) for the period April 1, 2014 to March 31, 2015 (FY2014). The annual product review includes the following intermediates and final products. The review included deviations, OOS, complaints, MA line (doxycycline) processes validation status, equipment qualification status, stability and stability deviations, change controls, and CAPAs.

Name	Internal Code	Number of Batches	Rejected	Reprocessed	Quantity (kg)
Doxycycline p-Toluenesulphonate (intermediate)	04MA62 05MA62-(repacking)	176 15	1 0	0	149140 10539
Doxycycline Hyclate	05MA51U	106	3	2	91248
Doxycycline Hyclate (Milled)	05MA51V	13	0	0	5306
Doxycycline Hyclate (Micronized)	05MA51M	4	0	0	194
Doxycycline Monohydrate	05MA64U	69	2	0	41116
Doxycycline Monohydrate (Milled)	05MA64V	25	0	0	5865
Doxycycline Monohydrate (Micronized)	05MA64M	19	0	0	4408

I reviewed the APR for Doxycycline Hydrate, Doxycycline Monohydrate, and Doxycycline Monohydrate (micronized) for the period April 1, 2013 to March 31, 2014 (FY2013). The review included deviations, OOS, review of manufacturing process changes, stability, process validation status, CAPAs, equipment qualification, production performance.

Name	Internal Code	Number of Batches	Rejected	Reprocessed	Quantity (kg)
Doxycycline p-Toluenesulphonate (intermediate)	05MA62-(repacking)	22	0	0	190,076
Doxycycline Hyclate	05MA51U	136	1	0	120,620
Doxycycline Hyclate (Milled)	05MA51V	12	0	0	3,961
Doxycycline Hyclate (Micronized)	05MA51M	0	0	0	0
Doxycycline Monohydrate	05MA64U	58	0	0	35,729

Doxycycline Monohydrate (Milled)	05MA64V	15	0	0	3,486
Doxycycline Monohydrate (Micronized)	05MA64M	12	2	2	3,005

For FY2013 and FY2014 there were no returns or recalls, and one complaint received in FY2014 which was reviewed.

No deficiencies were noted.

Out of Specifications

Procedure entitled OOS Investigation, HQ.CCO.COP015.6.EP, effective 18 May 2015 was reviewed. This procedure applies to any OOS obtained during testing of raw materials, packaging materials, recovered products, intermediate, finished products, stability samples, and OOT results.

I reviewed the following OOS from the period FY2013 to FY2015.

ID Number	Batch	Description	FY
28206	05MA64M; HM00036	OOS on Particle size result	FY2013
30147	05MA64M; HM00042	OOS on Particle size result	FY2013
36099	05MA51U; HM00804	OOS residual solvents by GC acetone result	FY2014
38993	05MA51U; HM00848	Description test OOS	FY2014
38184	05MA64U; HM00278 05MA64U; M00278.02	OOS pH, solubility and chloride test	FY2014
44591	05MA64; HM00057	Description test OOS	FY2015

There has been no OOS's for Doxycycline Monohydrate Micronized since Nov 2013. They have implemented an in-process sampling after the micronization step. If it passes the size specification then the process will continue to blending and packing. If the sample fails specification the micronization process will be repeated. The last OOS/deviation report number was 30147, dated 21 Nov 2013, due to Particle size failing. The particle size was 16µm and the specification is NMT 15µm.

Deviations

I reviewed procedure entitled Deviation Records, HQ.CCO.COP014.10.EP, and effective 01 Oct 2013. This procedure applies to quality and health, safety, environment (HSE) systems, procedures or instructions, manufacturing processes, test methods, protocols, OOS results, R&D projects, etc., for unexpected reasons or unforeseen circumstances are not performed or followed are called Deviation. Deviations are classified in terms of criticality (critical and non-critical), type and root-cause.

I reviewed the following deviations:

ID	Batch Number	Description	FY
46559	04MA62; HM03454	Atypical HPLC results observed	FY2015
46560	04MA62; HM03454 04MA62; HM03455	Atypical HPLC results observed for In process and in process samples	FY2015
37423	05MA51U; HM00829	Filtration (critical)	FY2015
36777	05MA51U; HM00815 05MA51U; HM00815.02	Atypical particle size distribution	FY2014
36179	05MA64U; HM00247 05MA64U; HM00247.02	Atypical particle size results observed	FY2014
38495	05MA64U; HM00284	Started without approval of process validation protocol	FY2014
40429	05MA51U; HM00871 05MA51U; HM00872 05MA51U; HM00873 05MA51U; HM00874 05MA51U; HM00875 05MA51U; HM00876	RV5004/RV402 used as washing tanks (qualified)	FY2015
42926	05MA51U; HM00901	Quantity of HCl weight verification not recorded	FY2015
47518	05MA51U; HM00952	Incorrect quantity of Ethanol charged	FY2015
43543	05MA64U; HM00323.02	One gray drum of wet product not loaded for drying	FY2015
46666	05MA64U; HM00183 – HM00343 (excluding 287-292, 298)	Second verification is missing in critical steps	FY2015

No deficiencies were noted.

Change Control

I reviewed Change Control procedure HQ.CCO.COP027.7.EN, effective 22 Dec 2014. The purpose of this procedure is to allow for assessment of the change, understanding, and documented and managed by the relevant areas to ensure changes are not implemented before approval. This procedure applies to any changes that may have an impact on health, quality, business, safety. Environment and Energy (HSEE), regulatory compliance, and R&D projects. Changes are classified under Major or Minor. The change control process has a preliminary process which is a pre-assessment of the change followed by six phases to include: 1) Description of the current system (with justification of proposed change), 2) Impact assessment of the change, 3) Implementation plan proposal, 4) Approval of the change proposal, 5) Evaluation after implementation, and 6) closure.

I reviewed the following change controls:

Change Control ID	Description	Date

7214	New Specification for Doxycycline Hyclate	24 July 2015
7098	Update current Doxycycline Hyclate specifications	28 May 2015
7087	New Specification for Doxycycline Monohydrate	26 May 2015
6924	Alternate equipment for Manufacturing 05MA64U	10 March 2015
6512	Rhodium reduction implementation	14 July 2014

No deficiencies were noted.

Reprocess/rework/returns

I reviewed the Procedure entitled Reprocessing, reworking, and returned products, HE.CCO.COP028.2.EN, effective 31 Oct 2015. This procedure defines the reprocessing, recovery and reworking and how it can and cannot be applied to manufactured products. Returns apply to all products supplied by Hovione with the exception of medicinal products already distributed to pharmacies, hospitals, and wholesalers. Returned products can be initiated by Hovione, clients, or agents to whom the product was distributed.

Rejection of intermediates and API's that fail to meet established specifications should be identified and segregated. These products may be submitted for reprocessing, reworking, recovery, or disposal depending on the process and on the regulatory filing.

According to the procedure reprocessing can occur when an intermediate or API does not conform to standards or specifications. Reprocessing is only permitted if it is done by repeating the same process used in manufacturing or other appropriate chemical or physical manipulations that are already part of the established manufacturing process to improve the quality to meet specification.

Recovery of Solvents

Recovered solvents from the mother liquor or filtrates of reactants, intermediates, or the API are acceptable as long as the recovered material meets specifications and follows procedures. Sampling of the distilled recovered solvent is performed every 24 hours by GC (IPC testing).

Rework

The firm does not perform reworking.

CAPAs

I reviewed procedure entitled CAPA System, HQ.CO.SOP030.4.EN, and effective date of 27 June 2014. They utilize a software application developed in house to track and manage all CAPA's. The processes that are handled in the CAPA system include: auditing, deviations, complaints, incidents, action plans, and HSE program specific events. The structured hierarchically is three levels: activity, event, and CAPA.

I reviewed the following CAPA's:

- CAPA ID: 36199, dated 31 Oct 2014, and closed on 18 Mar 2015, related to deviation report ID: 36099

- CAPA ID: 39112, dated 19 Mar 2015, and closed on 09 Apr 2015, related to deviation report ID: 38993
- CAPA ID: 39786, dated 15 Apr 2015, and closed on 30 Jun 2015, related to deviation report ID: 38993
- CAPA ID: 39788, dated 15 Apr 2015, and closed on 02 Nov 2015, related to deviation report ID: 38993
- CAPA ID: 40006, dated 29 Apr 2015, and closed on 09 Sept 2015, related to deviation report ID: 38993
- CAPA ID: 40007, dated 29 Apr 2015, and closed on 02 Nov 2015, related to deviation report ID: 38993
- CAPA ID: 40008, dated 29 Apr 2015, and closed on 08 May 2016, related to deviation report ID: 38993
- CAPA ID: 40014, dated 29 Apr 2015, and closed on 02 Nov 2015, related to deviation report ID: 38993

Stability Program

I reviewed procedure entitled Stability, HQ.CCO.COP024.7.EN, effective 31 March 2016. This procedure applies to API's, intermediate drug product and drug product under development or in commercial phase. It may also apply to raw materials if required. The Hovione stability program is managed via LIMS system. The stability program is to provide evidence on how the quality of the drug substance, intermediate drug product and drug product varies with time under the influence of a variety of environment factors such as temperature, humidity, and light, and to establish a retest period or shelf-life of finished products and to recommend storage conditions.

The firm provided a list of products shipped to the US with respective retest periods.

Material Code	Material Name	Retest Period (months)
05MA51U	Doxycycline Hyclate	36
05MA64U	Doxycycline Monohydrate	24
05MA64M	Doxycycline Monohydrate (Micronized)	24
05KB21	Ivermectin	24
[redacted]	[redacted]	60

I reviewed the stability study reports (accelerated and long term) for product shipped to US; [redacted] Ivermectin, Doxycycline Monohydrate (micronized), Doxycycline Monohydrate, and Doxycycline Hyclate.

The retest period is being continuously evaluated by the additional data from the ongoing stability program.

PRODUCTION SYSTEM (TXN)
Hovione (Macau's Site) manufactures both human and veterinary API products for domestic market (China) as well as international markets (Asia, Europe, Africa, Australia, South America, & United States). Currently, the firm manufactures the following API products for US market:

- Doxycycline Hyclate
- Doxycycline Hyclate micronized form
- Doxycyline Monohydrate
- Doxycyline Monohydrate micronized form
- Ivermectin
- [redacted]

The site manufacturing operations continue 24/7 with four teams rotating through three shifts:
Shift 1 8am 5pm
Shift 2 3pm 12am
Shift 3 11:30pm 8:30am

The production for Doxycycline Hyclate & micronized form, Doxycyline Monohydrate & micronized form, and Ivermectin are taken place in building 2A. The production for [redacted] is taken place in building 2.

Process Validation for Doxycycline Monohydrate Micronized: I reviewed the protocol and report related to process validation of micronized Doxycycline Monohydrate (Hovione's Internal Product Code: 05MA64M). The firm performed process validation using three batches HM00014 - HM00016. I reviewed the following documents related to process validation of micronized Doxycycline Monohydrate.

- Validation Protocol, Document: PV/08-017, Revision 0, Effective Date: December 25, 2008.
- Validation Report, Document: HM.QSR.PV109.0.EN, Approved Date: March 3, 2011.

Batch Number	QC Number
05MA64M.HM00014	AA-21772; CR-21773
05MA64M.HM00015	AA-34123; CR-34124
05MA64M.HM00016	AA-45493; CR-45494

The process validation data for micronized Doxycycline Monohydrate using the above three batches appeared adequate. No deficiencies were noted.

Commercial Batches: I reviewed the following commercial batches related to Doxycycline Monohydrate micronized and Doxycycline Hyclate.

Product Name & Code	Batch Number	Manufacturing Date	% Yield
Doxycycline Monohydrate Micronized, 05MA64M	HM00014	December 27, 2008	95.7%

Doxycycline Monohydrate Micronized, 05MA64M	HM00015	November 13, 2009	95.8%
Doxycycline Monohydrate Micronized, 05MA64M	HM00016	September 10, 2010	97.3%
Doxycycline Monohydrate Micronized, 05MA64M	HM00037	August 6, 2013	96.9%
Doxycycline Monohydrate Micronized, 05MA64M	HM00077	December 5, 2015	98.9%

The production records for the above batches appeared adequate and complete. No deficiencies were noted.

Line Clearance: The firm performs line clearance activities after and before the packaging process of each batch. Production employees used a check list to ensure that they have removed all of the tools and packaging materials related to the previous batch before starting a new batch. The production employees listed all of the tools and packaging components they brought inside the packaging room and the production supervisor will verified and signed off on the check list "Packaging Rooms Fixed Objects & Auxillary Utensils Control", Doc: HM.QSD.RF1141, Revision 1, Approved Date: Feb 27, 2014. I reviewed several line clearance activities and production batch records for Doxycycline Monohydrate Micronized and did not note any deficiencies.

Cleaning Procedure for Packaging Room: According to the firm's production manager, the firm cleans the room immediately after the packaging process of a batch is done. I reviewed a procedure titled "Cleaning Procedures for Packaging Rooms", Doc: HM.PR.IOP304, Revision 10, Effective Date: May 5, 2016. I also reviewed the cleaning records and documentation of several commercial batches of Doxycycline Monohydrate Micronized and did not note any deficiencies.

Cleaning Verification (Cleaning and Changing to New Product): The firm uses dedicated line to manufacture Doxycycline Hyclate, Doxycycline Monohydrate (including the micronized grades), and Ivermectin. The manufacturing process of Doxycycline Hyclate, Doxycycline Monohydrate, and Ivermectin are taken place in building 2 (using dedicated equipment). The manufacturing process for [redacted] occurred in building 2A (using shared equipment).

The firm does not have a cleaning validation study done on shared manufacturing equipment. Instead, they performed "cleaning verification" each time they switch over to a new API product. The firm has general and specific cleaning procedures for each type of manufacturing equipment (such as reactors, dryers, centrifuge, blenders, milling, sieving, transfer pipes, etc.). I reviewed the following cleaning procedures and cleaning verification data related to the switch-over of API product Roxythromycin (not distribute to U.S) to [redacted].

- Centrifuge, ID: 28FC010, "Cleaning Procedure and Cleaning Verification Procedure for Change of Line from Roxithromycin", Document: HM.CLN.PL00843, Approved Date: January 27, 2014.

- Dryer, ID: 29S020 (Bi4001), "Cleaning Procedure and Cleaning Verification Procedure for Change of Line from Roxithromycin", Document: HM.CLN.PL01102, Approved Date: July 23, 2015.
- Equipment Cleaning Evaluation of Carry Over/Maximum Allowable Carry Over and Individual Maximum Allowable Carry Over for Manufacturing Campaigns from Roxythromycin to [redacted] Document: HM.QSD.RF1040, Revision 2, Approved Date: September 30, 2014.

During this cleaning verification and evaluation process, the firm looked at equipment shared by the two products, cleaning level required for each type of equipment, cleaning solvent, calculation of the Maximum Allowable Carry Over for product and solvents, and compared the analytical results with the MACO values for the product and solvents. The entire records package is reviewed and released by QA before the release of the first batch after switching over to a new product. The firm's cleaning procedures and cleaning verification process is adequate. No deficiencies were noted.

Monitoring of Pressure Deferential in the Packaging Area: The firm maintained pressure differential in the packaging areas (inner core ~ 35-50 pascal, adjacent room ~25 pascal, and the airlock area ~12.5 pascal). The firm also trend fan speed, temperature, and relative humidity of the room(s) used during the packaging process. I reviewed the trending data during the packaging process of the following batches [redacted] to [redacted].

Equipment Qualification of Micronizer (Equipment Code: MZ201): The firm performed performance qualification of the micronization process using three batches of Doxycycline Monohydrate.

Starting Product/Batch No.	Micronized Product, Batch No.	Particle Size Result D (v, 0.9) = NMT10µm
05MA64U.HM00016	05MA64M.HM0005	All three batches meet particle size specification
05MA64U.HM00017	05MA64M.HM0006	
05MA64U.HM00020	05MA64M.HM0007	

I reviewed the following documents related to the qualification process of the micronizer.

- Global Qualification Protocol of New Micronizer (MZ201), Document: EQ/08-004, Revision 000, Effective Date: January 30, 2008.
- Design Qualification and Installation Report for Micronizer MZ201, Document: HM.QSR.EQ084.1.EN, Approval Date: March 4, 2010.
- Operational Qualification Protocol of Micronizer (MZ201), Document: EQ/08-006, Revision 0, Effective Date: February 21, 2008.
- Operational Qualification Report of Micronizer (MZ201), Document: EQ/08-010, Revision 0, Effective Date: May 23, 2008.
- Performance Qualification Protocol for Micronizer (MZ201), Document: EQ/08-007, Revision 1, Effective Date: March 28, 2008.

- Performance Qualification Report for 05MA64M (Doxycycline Monohydrate Micronized), Document: EQ/08-010, Revision 0, Effective Date: May 28, 2008.

The qualification process for Micronizer (Equipment ID: MZ201) used to produce Doxycycline Monohydrate micronized form appeared to be adequate. No deficiencies were noted.

Preventive Maintenance and Calibration of the micronizer, Equipment ID: MZ201: I reviewed the preventive maintenance log and calibration of temperature and pressure gauges of micronizer, equipment ID: MZ201. This equipment is used in the micronization process to convert Doxycycline Monohydrate (normal form) to Doxycycline Monohydrate micronized form (smaller particle size).

Micronizer, ID: MZ201	
Pressure Gauge, ID: PG19040	Calibrated Annually Last calibration was done on November 13, 2015
Pressure Gauge, ID: PG19050	Calibrated Annually Last calibration was done on November 16, 2015
Temperature Gauge, ID: TG19040	Calibrated Annually Last calibration was done on December 16, 2015

The preventive maintenance log and calibration certificates of pressure and temperature gauges related to micronizer, ID: MZ201 appeared adequate. No deficiencies were noted.

Equipment Qualification, Preventive Maintenance, and Calibration of the Double Cone Dryer/Blender (Equipment Code: Bi1601): The firm performed equipment qualification (IQ/OQ/PQ) for the Double Cone Dryer/Blender, Equipment ID: Bi1601 on October 30, 2004. They perform routine calibration of the temperature and pressure gauges in dryers every 6 to 12 months (depending on the type of sensor or gauge). The calibration of gauges was done in-house by the firm's engineering department.

According to the firm's management, the preventive maintenance of all major manufacturing equipment is scheduled in SAP system. The Double Cone Dryer (used in the manufacturing process of Doxycycline Monohydrate micronized) has 6 month & 12 months PM schedule. During the PM process of the dryer, the firm's engineer measured the electric current, condition of the chains, bearings, leaks, mechanical seals, insulation, electrical motor, thermal control, main shaft, and check for any abnormality observed on the equipment. The preventive maintenance of the double cone blender/dryer is done in-house by the firm's engineering department, but also done by "Pfaudler", the manufacturer of the equipment. I reviewed the maintenance service records of the double cone dryer done by Pfaudler dated July 5, 2015. During the preventive maintenance, Pfaudler's service technician verified that the dryer is in good working condition; glass lining is still in good conditions, no damages found with seals and abnormal noises/vibrations noticed. I reviewed the qualification process (IQ/OQ/PQ) and documents protocol & report, Document No: EQ/04-050, Revision: 000, Approved Dated:

10/30/2004 related to double cone dryer/blender, ID: Bi1601. Below is the specification and information related to the dryer:

Double Cone Dryer/Blender (ID: Bi1601)	
Height	1533mm
Diameter	1100mm,
Weight	755 kg
Rotation Speed	1.6 to 9.6 rpm
Temperature	-10C to 200C
Pressure in Storage Tank	-1 bar to +3 bar
Calibration of Temperature Sensor, ID: TE05010	Every 6 months Last calibrated: January 13, 2016.
Calibration of Pressure Gauge, ID: PG05010	Annually Last calibrated: July 8, 2015

The firm's qualification process and supporting data for the double cone dryer/blender appeared adequate. No deficiencies were noted.

Preventive Maintenance and Calibration of Manufacturing Equipment: I reviewed the preventive maintenance for the following manufacturing equipment.

Equipment Name & ID	PM Interval	Test Perform
Glass Lined Reactor, ID: RV6003	12 months	Thickness

No deficiencies were noted.

Environmental Monitoring: The firm performs air particle count and active microbiological air sampling in the packaging areas every three months. For all US products, they are packed in ISO 9 room. The limits for airborne particle Count (0.5 µm and 5 µm) and limit for Total Bacteria and Fungi ($\leq 200 cfu/m^3$). I reviewed the following procedures related to environmental monitoring.

- Environmental Control, Doc: HM.CO.IOP013, Revision 8, Approval Date: October 8, 2015
- Microbial Air Quality Control, Doc: HM.MI.TG2791, Revision 2, Approval Date: June 17, 2015
- Annual Environmental Report FY 2015, Doc: HM.QSR.RE606, Revision 0, Approval Date: May 5, 2016.

The firm's environmental monitoring procedure and annual report appeared adequate. No deficiencies were noted.

In-Process Control (IPC) Parameters for the Micronizer during the micronization process of Doxycycline Monohydrate: The firm uses following parameters to run the micronizer. According to the Head of Production, the parameters listed below are the optimal setting to run the micronizer and the values came from process validation.

Step	Parameter	Setting Values
01	Pressure [redacted]	[redacted]
	Pressure [redacted]	
	Feeding rate [redacted]	

LABORATORY SYSTEM (TXN)

The firm's quality department consists of 38 full-time employees (30 in QC and 8 in QA). The Head of Quality Assurance is Mrs. Rainbow Chung. The Head of Quality Control Unit is Mr. Neilson Lio. The firm's QC department consists of both chemistry and microbiology laboratories and capable of performing testing for raw materials, intermediates, finished products, stability studies, water, and environmental monitoring. The firm's quality department use LIMS (Laboratory Information Management System). All chromatographic instruments such as Gas Chromatography, HPLCs, FT-IR, and Malvern Mastersizer (particle size analyzer) are connected to a centralize server and being backup daily.

Test Record Review: I reviewed the test record packages for the following batches/products:

Product Name & Code	Batch Number	Sample Number ID	Test Performed & Release Date
Doxycycline Monohydrate Micronized, 05MA64M	HM00014	AA-21772 (Wet Chemistry) CR-21773 (Chromatography)	Wet Chemistry: pH, Water Content, Bulk Density, Crystallinity, Description, & Particle Size Chromatography: Residual Solvents (GC) Acetone & Ethanol, Content of Triethylamine, Assay (HPLC), Related Substances, Identification (HPLC), Other Impurities, & Total Impurities.
Doxycycline Monohydrate Micronized, 05MA64M	HM00015	AA-34123 (Wet Chemistry) CR-33453 (Chromatography)	Wet Chemistry: pH, Water Content, Bulk Density, Crystallinity, Description, & Particle Size Chromatography: Residual Solvents (GC) Acetone & Ethanol, Content of Triethylamine, Assay (HPLC), Related Substances, Identification (HPLC), Other Impurities, & Total Impurities.
Doxycycline Monohydrate Micronized,	HM00016	AA-45493 (Wet Chemistry)	Wet Chemistry: Residue on Ignition, Identity (IR), Specific Rotation, pH, Water Content, Chloride, Heavy Metals, Particle Sizes, Bulk

05MA64M		CR-45494 (Chromatography)	Density, Crystallinity, Solubility, Ultra Violet/Vis Absorption, Description, Identification (reaction with Sulfuric Acid), & Light Absorbing Impurities. Chromatography: Residual Solvents (GC) Acetone & Ethanol, Content of Triethylamine, Assay (HPLC), Related Substances, Identification (HPLC), Other Impurities, & Total Impurities.
Doxycycline Monohydrate Micronized, 05MA64M	HM00037	AA-100990 (Wet Chemistry) CR-100991 (Chromatography)	Wet Chemistry: Residue on Ignition, Identity (IR), Specific Rotation, pH, Water Content, Chloride, Heavy Metals, Particle Sizes, Bulk Density, Crystallinity, Solubility, Ultra Violet/Vis Absorption, Description, Identification (reaction with Sulfuric Acid), & Light Absorbing Impurities. Chromatography: Residual Solvents (GC) Acetone & Ethanol, Content of Triethylamine, Assay (HPLC), Related Substances, Identification (HPLC), Other Impurities, & Total Impurities.
Doxycycline Monohydrate Micronized, 05MA64M	HM00077	AA-148613 (Wet Chemistry) CR-148614 (Chromatography)	Wet Chemistry: Residue on Ignition, Identity (IR), Specific Rotation, pH, Water Content, Chloride, Heavy Metals, Particle Sizes, Bulk Density, Crystallinity, Solubility, Ultra Violet/Vis Absorption, Description, Identification (reaction with Sulfuric Acid), & Light Absorbing Impurities. Chromatography: Residual Solvents (GC) Acetone & Ethanol, Content of Triethylamine, Assay (HPLC), Related Substances, Identification (HPLC), Other Impurities, & Total Impurities.

I reviewed several test procedures including sample and standard preparation, lab logbooks, notebooks, and worksheets. I verified some of the test results again raw data, chromatograms, and calculations. The above test records appeared accurate, complete, and adequate. No deficiencies were noted.

System Suitability: According to the Head of Quality Control, the firm performs system suitability prior to run each HPLC & GS analysis. I verified that the lab performs system suitability run for the above test sample. System suitability for HPLC analysis normally consists of 5 or 6 injections of the standard solution (%RSD $\leq$ 2.0%). Of course system suitability requirement is different depending on the test method. No deficiencies were noted.

Test Method Validation/Verification: I reviewed the test method validation packages for Assay and Related Substances of Doxycycline Monohydrate.

- Validation Protocol for "Doxycycline Monohydrate Micronized Assay & Related Substances by HPLC", Document: HM.QSP.MV372, Approved Date: September 30, 2011.
- Validation Protocol for "Doxycycline Monohydrate Micronized Assay & Related Substances by HPLC", Document: HM.QSR.MV756, Approved Date: November 11, 2011.

The firm performed method verification against USP method. During test method verification, the firm evaluates using the following criteria: Selectivity, System Precision (System Suitability, 5 injections, %RSD ≤2.0%), Repeatability, LOQ (Quantitation Limit), LOD (Detection Limit). There were no deviations occurred during method verification process. All test results were within specification limit. No deficiencies were noted.

Residual Solvent: I reviewed method validation for Residual Solvent of Acetone and Methanol by Gas Chromatography in Doxycycline Monohydrate.

- Validation Protocol for Determination of Acetone and Methanol by GC in (05MA64U Doxycycline Monohydrate) and (05MA64M Doxycycline Monohydrate Micronized), Document: HM.QSP.MV367, Approved Date: April 3, 2012.
- Validation Report for Determination of Acetone and Methanol by GC in (05MA64U Doxycycline Monohydrate) and (05MA64M Doxycycline Monohydrate Micronized), Document: HM.QSP.MV835, Approved Date: June 1, 2012.

The firm developed this method in-house and the validation includes the following criteria: Selectivity, Linearity & Range, Accuracy, Precision, Repeatability, Intermediate Precision, Reproducibility, Limit of Quantitation (LOQ), Limit of Detection (LOD), and Robustness. The system suitability for this test method is done with 6 injections of "standard solution 3" with %RSD = NMT 10.0%. There were no deviations occurred during the method validation of this method. All test results were observed to be within specification limit. No deficiencies were noted.

Equipment Qualification (IQ/OQ/PQ) of the Malvern Masterizer, ID: MV3/A: The firm uses this instrument to measure the particle size of Doxycycline Hyclate (Product Codes: 05MA51U & 05MA51M) and Doxycycline Monohydrate (05MA64U & 05MA64M) micronized. This equipment was transferred to the Macau's site from Novione Headquarter office in 2010. The firm's QC lab only has one Malvern Masterizer. The initial qualification of the Malvern Masterizer (IQ/OQ/PQ) was done by Malvern's engineer. The performance qualification of the Malvern was done using two different API products each used three batches. Please refer to the table below:

Product Name & Code	Batch Number	Test Performed
Doxycycline Monohydrate Micronized, 05MA64M	HM00005	Repeatability, Intermediate Precision, Reproducibility, System Suitability & Accuracy
Doxycycline Monohydrate Micronized, 05MA64M	HM00011	There were no deviations occurred during the

Doxycycline Monohydrate Micronized, 05MA64M	HM00014	IQ/OQ/PQ. All test results met specifications.
Roxithromycin, 05ML01V	HM00011	Repeatability, Intermediate Precision, Reproducibility, System Suitability & Accuracy There were no deviations occurred during the IQ/OQ/PQ process. All test results met specifications.
Roxithromycin, 05ML01V	HM00016	
Roxithromycin, 05ML01V	HM00017	

Annual calibration of the Malvern was done in-house by qualified analysts. The calibration of the Malvern was done using PS 62 Reticle (Certified Standard purchased from Malvern). The PS 62 Reticle is certified by Malvern every two years. The last calibration of the Reticle is done on September 21, 2015 and will expired on September 21, 2017. Particle size is measure based on laser diffraction principle. The firm used qualified batch of micronized Doxycycline monohydrate as the reference standard and perform system suitability of the Malvern each day prior to performing particle size analysis. The sample is analyzed three times and takes the average result. All data related to the particle size analysis is captured and saved onto a centralize network. All analysts are required to use individual login name and password to access the Malvern Masterizer system.
The last annual calibration of the Malvern instrument was done in-house using Internal Operating Procedure (IOP), Reference: HM.QSD.TC055 on November 24, 2015. No deficiencies were noted.

Preventive Maintenance of the Malvern Masterizer: The firm uses a procedure titled "MV3/A Functional Instructions", Document: HM.QSD.IF396, Revision 1, Approved Date: October 19, 2015 to perform routine maintenance of the Malvern system. The procedure outlines how to use the instrument, cleaning, and maintained the Malvern. The procedure also describes how to dissemble and clean the dispersion cell and lenses and install it back into the instrument. I reviewed a maintenance logbook, ID: MV3/A, logbook #1 related to the Malvern Masterizer, ID: MV3/A. No deficiencies were noted.

Qualification of Agilent HPLC (DQ/IQ/OQ/PQ), Equipment ID: LC13/C: The firm's QC lab has 9 Agilent HPLCs. All of the HPLCs are connected to Empower 3 network & LIMS. I reviewed the following documents related to the qualification of the above HPLC.

- Equipment Qualification Protocol, Document: HM.QSP.EQ302, Approved Date: May 8, 2014
- Equipment Qualification Report, Document: HM.QSR.EQ335, Approved Date: August 1, 2014

The equipment qualification of this HPLC was done by Agilent's Service Engineer. During the qualification process, the firm checked the pump, degasser, auto sampler, column, detector, pump accuracy, temperature accuracy, wavelength accuracy, noise to drift, injection precision, and carry over. There were no deviations occurred during the qualification process. No deficiencies were noted.

Qualification of Agilent GC with Headspace (DQ/IQ/OQ/PQ), Equipment ID: GC6/C: The firm's QC lab has two GC systems. One of the GC systems is equipped with a headspace and one is not. The initial qualification of both GC systems was done by Agilent's service engineer. I reviewed the following documents related to the qualification of Agilent GC with Headspace (DQ/IQ/OQ/PQ), Equipment ID: GC6/C.

- Equipment Qualification Protocol, Document: HM.QSP.EQ109, Approved Date: December 3, 2009.
- Equipment Qualification Report, Document: HM.QSR.EQ128, Approved Date: December 23, 2009

The equipment qualification of this GC was done by Agilent Engineer. During the qualification process, the firm checked the GC Oven Accuracy and Stability, Inlet Pressure Accuracy, Detector Flow Accuracy, Signal Noise and Drift, and Injection Precision. There were no deviations occurred during the qualification process. No deficiencies were noted.

Qualification of Stability Chamber (Accelerated Chamber, ID: EH6) at 40°C ±2°C and 75%RH ±5%

- Qualification Protocol for Stability Chamber, Document: HM.QSP.EQ552, Approved Date: December 14, 2015.
- Qualification Report for Stability Chamber, Document: HM.QSR.EQ391, Approved Date: March 11, 2016
- Assessment on Changing the Humidity Setting on EH6 from 75%RH to 70%RH, Document: HM.QSR.RE622.0.EN, Approved Date: May 14, 2016.

During the qualification process, the firm performed DQ/IQ/OP/PQ. The firm verified temperature range and tolerance, humidity range and tolerance, chamber volume, alarm system, temperature and humidity data storage and retrieval, local display, operating environment. The firm performs temperature mapping for empty load and full load using calibrate data loggers. The firm also performed reliability study which lasted to seven days. The firm also performed daily check on the chambers three times each day (once every shift morning, noon, & at night).

Preventive Maintenance and Calibration of Laboratory Instruments: The firm's has specific written procedure used to perform preventive maintenance and calibration for each type of lab instrument. I reviewed the following procedure related to the Preventive Maintenance and Calibration of laboratory instruments:

- Calibration of HP Agilent HPLC system, Document: HM.QSD.TC050, Revision 6, Date: August 9, 2013
- Calibration of Agilent GC system, Document: HM.QSD.TC065, Revision 2, Date: January 29, 2013
- Balance Calibration, Document: HM.QSD.TC082, Revision 3, Date: October 29, 2015

- Calibration Technique for FT-IR2/A, Document: HM.QSD.TC101, Revision 1, Approval Date: October 29, 2015

I also reviewed the preventive maintenance records and routine calibration of the following lab instruments/equipment.

Equipment Name & ID	PM Interval	Test Perform
Agilent GC, ID: GC6/C	Calibrate in-house every 6 months Last calibration done on Feb 5, 2016 for GC and Headspace done on Feb 27, 2016	Temperature testing of oven, Flow control Verification, and Headspace Injection Precision
Agilent HPLC, ID: LC13/C	Calibrate in-house every 6 months Last calibration done Feb 5, 2016	Calibration of Detector, Wavelength Accuracy, Lamp Intensity, Pump, Flow Rate, Gradient Composition, Thermostatted Autosampler, Column Heat Exchanger, Injection Precision.
Incubator, ID: IC2/M	Calibrate in-house Quarterly Last Calibration Date: April 18, 2016	
Analytical Balance, ID: BL9/A	Calibration is done in-house monthly, bi-annually, and annually. Last calibration done on May 4, 2016 The firm performs daily verification of the balances using traceable standard weights.	Use various standard weights to check the balance.
FT-IR, ID: FTIR2/A	Calibration is done in-house monthly Last calibration was done on May 4, 2016	Check wavelength and resolution

The preventive maintenance and calibration for the above instruments/equipment appeared adequate. No deficiencies were noted.

Training: According to the QC manager, most of the lab equipment qualification is done by the vendors. Some of the ongoing calibrations of instruments/equipment are done in-house by qualified personnel. The firm also uses the vendor services for maintenance and calibration depending on the complexity of the task. The qualified personnel have many years working in the lab and also received training from the vendor such as Waters and Agilent.

The firm uses an electronic training program called TrainStream to implement new/revised SOPs and to document training events. The lab also performs assessment test to evaluate the competency of their analysts. Assessment tests are usually conducted by Technical Coordinator. I reviewed several training records from employees working in the QC lab. No deficiencies were noted.

OOS Related to Micronization Process: According to the firm's management, there has been no OOS related to micronization process of Doxycycline Monohydrate micronized since November 2013. The firm does have other OOSs related to raw materials and finished products listed section under Quality System.

System Security, Access, and Back-up: According to the firm's management, all analytical systems such as HPLC, GC, FT-IR, and Malvern are connected to a centralize server and LIMS. I verified that analytical systems such as HPLCs, GCs, FT-IR, and Malvern Masterizer required individual login name and password to gain access. The passwords are required to change every 90 days. The firm uses Agilent GC & HPLC systems. However, all of these chromatographic systems are connected to Empower software to store and process chromatographic data. Both chemistry and microbiology labs use LIMS (Laboratory Information Management System). LIMS is also connected to the SAP system to release raw materials and finished products. According to the firm's management, both of LIMS and SAP were implanted since April 2007. According to the Head of QC department, the firm has recently upgraded their chromatographic data acquisition from ChemStation to Empower since September 2015. I reviewed and confirmed that chromatographic project folders are created by IT department, and analytical data are stored in designated folder. I reviewed multiple project folders and confirmed that audit trail features are enabled. The firm's has a program in place to check the audit trail after each HPLC and GC run. Quality unit also have program to check the audit trail every 6 & 12 months. Analytical data is being back up throughout the day onto a centralized server. The IT department also performed "hard back up" week/monthly according to a predefined schedule.

Water System: The firm produces two types of water (softening water and Deionized water) used to clean equipment and in some stages of the manufacturing process (for example: Doxycycline Monohydrate Process used deionized water during the crystallization process). There are 24 points of use (15 points are used as raw material and being test regularly, the remaining 9 are used for cleaning the floor and non-critical equipment). The 15 points are being tested every four weeks. Point #39 is used to make the Deionized Water. The firm sanitizes the entire water system once every three weeks. The firm performs the following tests in-house:

- Description
- Content of Free Chlorine
- Content of Calcium
- Conductivity
- Bacteriological Analysis Sulfite-Reducing Clostridia
- Bacteriological Analysis Coliforms

- Bacteriological Analysis Streptococcus
- Total Aerobic Count (NMT 100cfu/ml)

The Alert Limit for the deionized water system is ≥ 50 cfu/ml

I reviewed the water monitoring report for the past two years. Annual Water Report for 2014 (HM.QSR.RE527 Approved Date: September 7, 2015). Annual Water Report for 2015 (HM.QSR.RE605, Approved Date: May 6, 2016). All test results were within specifications. No deficiencies were noted. I reviewed the raw data logbook for water testing "Water Analysis, Log-Book No. 41". No deficiencies were noted.

Sanitization of the Water System: the firm sanitizes their entire water system every 21 days using 10% Sodium Hypochlorite solution. The sanitization solution stays in the system for 12 hours. After 12 hours, the firm flushed the entire system with clean softening water for at least 35 minutes. The firm performed validation study on the sanitization process of the softening and deionized water systems to show that they are able to remove contaminants and cleaning reagent to an acceptable level (<1.5ppm Chlorine). The firm selected several sampling points based on worst case scenario (lowest, highest, and longest points) to show that all test points are below acceptable limits. I reviewed the Softened Water System Purging time report, Doc: HM.QSR.RE436, revision 0, Approved Date: December 31, 2013. I also reviewed the "Soften Water System Logbook, No. 10). All test data were observed to be within specifications. No deficiencies were noted.

Microbiology Lab: The firm purchased culture media from Merk and performed Growth Promotion Test on each batch of media prior to use for testing (including positive and negative control). The firm's microbiology lab is relatively small and capable of performing limited tests such as environmental monitoring (air particle count & settling plates), Total Bacterial Count, and water testing. I reviewed the following growth promotion for R2A & SPS, Endo, AZIDE (for water testing) and Environmental Control (TSA, SDA, and Contact Plate).

R2A Growth Promotion Test: I reviewed a procedure titled "Culture Media: Growth Promotion Testing", Doc: HQ.MI.MC002, Revision 10, Approved Date: April 19, 2016. I reviewed the GPT test for R2A, lot 135834, validity date: March 26, 2016. The GPT test was performed on January 29, 2016 and data is capture in "Quality Control Department Growth Promotion Test, Logbook No. 1". The R2A media, lot 135834 support growth. The firm's procedure and data appeared adequate. No deficiencies were noted.

TSA Growth Promotion Test: I reviewed a procedure titled "Culture Media: Growth Promotion Testing", Doc: HQ.MI.MC002, Revision 10, Approved Date: April 19, 2016. I reviewed the growth promotion for TSA, lot #135777, Validity date: June 20, 2016. The GPT test was performed on January 29, 2016 and raw data were captured in logbook "Quality Control Department Growth Promotion Test, Logbook No. 1". The media support growth. No deficiencies were noted.

MATERIALS SYSTEM (SAW)

I reviewed the Procedure entitled Quality Control of Products, HQ.CCO.COP017.5.EN, effective 18 Oct 2014 and Procedure entitled Sampling procedures for raw materials, packaging materials, intermediates and finished products, HM.CO.SOP017.2.EN, effective 04 May 2015. The Quality Assurance Technical Coordinator, Ms. Nunes and Ms. Chung explained the procedures to me.

This procedure applies to Manufacturing, Warehouse, Quality Control Unit, and Quality Assurance Unit whenever it is necessary to sample and approve/reject materials, packaging materials, in-process control (IPC), recovered products, intermediates and finished products. The number of containers to sample from each lot is calculated from the formula $\sqrt{n} + 1$. If there are less than 4 containers then all containers are sampled. All sampled drums/packages are marked with an S and are recorded in a log book.

When possible, a visual inspection is also completed of the product for abnormal color, sediments or layering in the case of liquids, or foreign material or of unusual size. Sampling tools used are marked "Clean and Inspected" and signed and dated for the purpose of sampling. Sampling tools are cleaned in the QC laboratory. All sample labels are printed from LIMS and are checked against the SAP label on the original container.

Identification testing is performed by two tests. I reviewed the Check List for batch number by Quality Control batch number 0102716.HM01055, product Methacycline Hydrochloride along with the Analysis Requests and Results.

The minimum retention period for retention/reserve samples are as follows:

- One year:
    - Raw materials and intermediates other than solvents, gases, water or hygroscopic, deliquescent or degradable products.
- Expiry/retest date + 1 year or 3 years after distribution of the batch, whichever is longer.
    - API

Warehouse staff receives materials in a designated receiving area in front of the Raw Materials Warehouse. Data is verified and recorded on the Chemical Products Reception Document or Goods/Services Receipt Form. The COA is compared for chemical products as well as the condition of the materials received which may include:

- Product name on label, Product Lot, and Batch number
- Vendor/Manufacturer
- Purchase order number
- Legibility of the label
- Quantity per container and total quantity
- Number of containers per lot/batch
- Any damage to the container or seal

- Any change on the connection valve for gas cylinder
- Re-evaluation date
- COA/ conformity
- Safety instructions/safety data sheet (if applicable)

After receipt of goods has been completed, the goods are entered into the Systems Applications and Products (SAP). SAP will print out the identification labels. A Hovione batch number will be assigned to each single vendor batch for each delivery. If there are any damaged containers those containers receive a separate Hovoine batch number.

I reviewed the HM Rainbow Validation Master Plan, HQ.IS.VP010.0.EN, effective 18 Dec 2006, for the roll-out of SAP system and implementation of LIMS, and the Go-live report, HQ.IS.GLR010.1.EN, dated 04/2007, and HM Rainbow Final Validation Report, HQ.IS.FVR008.0.EN, dated July 2007.

I reviewed a Packaging/Chemical Products Receiption checklist and a Warehouse Goods Receive Checklist for Methacycline Hydrochloride batch [redacted]. This raw material is used for production of Doxycycline.
These checklists included material verification, documents verification, physical verification, weights, and SAP reception and labeling information.

The controlled temperature areas include CR4 which houses Avermectin (raw material), purified Avermectin, and wet Ivermectin. This temperature storage is -12°C to -18°C. The finished product warehouse which houses all finished products and has a temperature limit of 25°C and a relative humidity limit of 65%. And the intermediate warehouse which mainly houses the intermediate Doxycycline p-Toluenesulphonate and is kept at the same temperature as finished products. All temperature regulated areas are connected to the DCS System. The data is checked and trended.

I reviewed the following Operating Procedures with regards to storage of materials:

- Standard Instructions for Groups 1 and 3, HM.WH.IOP002.22.EN, effective 14 May 2016.
- Standard Instructions of Intermediate Products Warehouse, HM.WH.IOP003.11.EN, effective 14 May 2016.
- Standard Instructions of Finished Products Warehouse, HM.WH.IOP004.16.EN, effective 14 May 2016.

Supplier Qualification

I reviewed the two suppliers of the starting material for the intermediate of Doxycycline, MA62. They requalify the suppliers every three years by an onsite audit. I reviewed the quality agreement for the two suppliers. Each of the quality agreements has a detailed description of responsibilities between the supplier and Hovione along with the specifications of the material, process flowchart and manufacturing locations, test methods and locations, packaging and labeling, subcontracting, TSE declaration, Melamine declaration, declaration on Jatropha Plant usage, complaint report, and history of changes. The material name is Methacycline Hydrochloride and the two suppliers are:

[redacted]

The last onsite audit to [redacted] was completed in March 9, 2016 and found acceptable.

[redacted]

The last onsite audit to [redacted] was April 27, 2016 and found acceptable.

PACKAGING & LABELING SYSTEM (SAW)

I reviewed the operating procedure entitled Packaging and Labeling, HM.CO.SOP021.5.EN, effective 06 Nov 2015 and Ms. Chung explained to me the labeling process. After goods are checked in, the warehouse personnel prints out identification labels issued from the SAP system for each unit or package and an extra label is printed out to place on the Chemical Products Reception Document or Goods/Service Receipt Form.

A second Warehouse employee verifies the information on the labels, signs and dates them and affixes the labels to the containers or packages. SAP communicates with the Laboratory Information Management System (LIMS) which generates the required information for the sampler to sample the product. All analytical information is available in LIMS. Once the sample passes testing, QC will approve the batch and enter the information into the LIMS system. The SAP system will unrestrict the material for use once that is completed.

When a label is reissued (e.g.: for change of location) the previous label should be maintained visible on the packaging, and be crossed, initialed and dated, and be affixed in close proximity to the previous one.

The types of Labels include:

Type	Color
Identification	White
Rejected	Red and White
Transit within the plant	White
Export/Shipping	White
Secondary products or waste	Yellow
Samples	White
Returned Product	White
Transport and handling	Variable

The finished product primary packaging can include:

- High density polyethylene flasks
- Low density polyethylene bags
- Aluminum laminate bags

The secondary packaging can include:

- Aluminum laminate bags
- Aluminum tins
- High density polyethylene drums
- Fiber drums

I reviewed the Operating Procedure entitled, Packaging and Identification Labeling, NJ.CCO.COP021.2EN, effective 31 March 2016.

The firm provided a label for the product Doxycycline Monohydrate (Micronized) USP shown in **Exhibit SAW – 4**.

The Packaging & Labeling System had no deficiencies noted.

MANUFACTURING CODES (SAW)

An example of the lot numbering system for finished products: batch #: **05MA64M.HM00082**

The first part of the batch number consists of a two-digit material group number + a material code:

05 Material group code, where 05 represents the finished product.
MA64M An alpha-numeric material code. MA64M refers to Doxycycline Monohydrate (Micronized).

The second part of the batch number consists of two letters representing where it was manufactured followed by a five digit sequential number.

HM Represents the site where the batch was produced, or Hovione Macau.
00082 Is a 5-digit sequential number.

The lot number is documented on the batch production record, the label, and the certificate of analysis.

The firm's internal codes for products produced are:

Doxycycline Hyclate 05MA51U
Doxycycline Monohydrate 05MA64U

Doxycyline Monohydrate (Micronized) 05MA64M
Ivermectin 05KB21
[redacted]

COMPLAINTS (SAW)

I reviewed procedure entitled, Handling of Complaints, HQ.CCO.COP029.7.EN, effective 22 Dec 2014. This procedure applies to any complaints received by a Hovione site related to product quality or services rendered, and health, safety and environment (HSE). Each complaint investigation has a description, investigation, root causes, assessment of quality impact, CAPAs, and conclusion/observations. There were a total of eleven complaints for the period of January 2013 to April 2016. All complaints were investigated and closed. There were no deficiencies noted in the compliant handling system.

I reviewed the following complaints:

Complaint Number	Product and Batch #	Date of Complaint	Reason
26075	05MA64M; HM00032 05MA64M; HM00033	27 March 2013	Material code on drums was incorrect. The material code was overlooked. The correct material was delivered to buyer. They have included more on the verification step before printing of labels. One label will be printed and verified before the rest are printed. Three CAPAs initiated. Closed May 9, 2013.
29284	[redacted] HM00069	03 October 2013	Foreign particle observed. It was identified as black polypropylene. A broken cap seal fell on reactor. Three CAPA's were initiated that focused on prevention measures. Closed 09 December 2013.
35330	[redacted] HM00093	24 September 2014	Drum overweight. Root causes were the electrical cable and power adapter because of cable shifts and the verification process is not well defined in [redacted] packing instructions. Five CAPAs were initiated. 17 December 2014
37267	05MA64U; HM00234.02	17 December 2014	Black foreign material observed. Probable root cause was due to excessive feeding from the dryer to the sieving device. Accumulated product may have been stuck and continuously being heat stressed by rotation of the device. Decomposed product fell from sieving device resulting in black particles found. Four CAPA's implemented. Closed on 6 July 2015.
40916	05MA51U; HM00851.02	11 June 2015	Black foreign material observed. Due maintenance and aging of equipment and awareness of staff of the operation. Two CAPAs were implemented. Closed on 11 Sept 2015.
42829	05MA51U; HM00750.02	17 September 2015	Weight discrepancy on one drum. Error in weighing product. They have improved the weighing verification record of the Batch Production Record. Three CAPAs were initiated. Closed on 30 November 2015.
44416	05KB21; HM00073	25 November 2015	One container received with one large bag and 20 small bags. Due to misunderstanding of written packing order. They

	Ivermectin		created a new packing order template. Three CAPAs were initiated. Closed on 28 January 2016.

No issues were found with how the firm documented and investigated complaints.

RECALL PROCEDURES (SAW)

The firm has not had to perform any recalls since the last inspection. I reviewed procedure HQ.CCO.COP030.1.EN, entitled Product Recalls, effective 09 March 2011. This procedure applies to API or finished product supplied by Hovione that have been already distributed by Hovione customers to pharmacies, hospitals, or any wholesalers of those entities for which quality issues with potential health hazards were identified after product distribution by Hovione, customers, or health authorities.

The firm has not had any recalls.

REFUSALS

We did not encounter any refusals during the course of this inspection.

ADDITIONAL INFORMATION (SAW)

Lodging Accommodations
We stayed at The Landmark Macau. The hotel was about a 20 minute drive to/from the firm. Breakfast was not included and the room had very minimal closet space. However, the hotel offered many amenities including a nice gym and pool, money exchange, free shuttle bus to other hotels, and was walking distance to restaurants and grocery shopping.

SAMPLES COLLECTED

No samples were collected.

EXHIBITS COLLECTED

SAW – 1	List of Consignees, 1 page.
SAW – 2	List of shipped products to U.S., 9 pages.

SAW – 3	HM Organizational Chart, 1 page.
SAW – 4	Doxycycline Monohydrate (Micronized) Label, 1 page.

ATTACHMENTS

No attachments are included.

Stacie A. Woods -A

Stacie A. Woods, Investigator

Truong X. Nguyen -S

Truong X. Nguyen, Investigator