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

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Division International Drug Quality
International Compliance Branch
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May 31, 2013

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

Reference: FEI 3002807210

Dear Mr. Leong:

We have completed our review of the Establishment Inspection Report (EIR) for the inspection conducted at your Active Pharmaceutical Ingredients manufacturing facility in Taipa, Macau, by Investigator Jose R. Hernandez during the period of January 28-30, 2013.

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

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

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

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

Sincerely,

Christina Alemu-Cruickshank

Christina Alemu-Cruickshank
Compliance Officer
Division of International Drug Quality

Enclosure: EIR

TABLE OF CONTENTS

SUMMARY

This was a routine GMP inspection of this producer of Active Pharmaceutical Ingredients (Profile class CSN). This inspection was given FACTS assignment #8124912 and Operation Code #63633878, and filed under TUBO EIR #322671. The inspection was conducted as scheduled by the ORA/Division of Medical Products and Tobacco Inspections (DMPTI), trip #2013-094D. There was no EES assignment associated with this inspection. FDA trip coordinator and CDER were informed of the results of the inspection (**Attachment 1**).

Inspectional coverage was given under Compliance Program 7356.002F- Active Pharmaceutical Ingredient (API) Process Inspection and CP7371.001 – Post Approval Monitoring of Animal Drugs (PAC# 71001B). ICH Q7A was used as a guide. This was a qualified system inspection.

The firm has been inspected by FDA on six previous occasions with the last inspection conducted in June 2009. The 2009 inspection was a team (Investigator/Analyst) inspection covering all six

systems. That inspection uncovered some observations. The firm responded to the cited observations by letter dated July 21, 2009 with corrective actions being satisfactory. The EIR was classified VAI.

The **current inspection** disclosed no inspectional observations. No FDA-483 was issued. No sample was collected. No refusals were received during the inspection.

ADMINISTRATIVE DATA

The inspection was coordinated by ORA/Division of Medical Products and Tobacco Inspections (DMPTI). No FDA-482, Notice of Inspection, was issued since this was a foreign inspection.

At the onset of the inspection, official credentials were presented to Mr. Eddy Leong, General Manager, and most responsible person for the factory. Mr. Leong and persons mentioned below were present and or provided information for this report.

Mrs. Rainbow Chung, Head of Quality Assurance

Mr. Johnny Cheong, Production Director

Ms. Andreia Borges, QA Technical Coordinator

Mrs. Jenny Fong, Head of Quality Control

Mr. Bowie Soe, Head of Production

Mr. António Cotão, Head of Warehouse

Persons present representing the corporate office located in Portugal.

Mr. José Lisboa, Corporate QA Director

Mrs. Luisa Paulo, Compliance Director

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:	1/28/2013, 1/29/2013, 1/30/2013
Days in the facility:	3
Participants:	Jose R. Hernandez, Investigator

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

Hovione PharmaScience Limited (HM) is one of the companies of the Hovione Group. The Hovione Group is an international group dedicated to the development and manufacture of APIs for the pharmaceutical industry. The Hovione Group was established in Portugal in 1959 and has several offices around the world including five industrial sites. The inspected site is located Estrada Coronel Nicolau De Mesquita, Taipa, Macau.

Hovione headquarters' address is: Hovione FarmaScience SA, Sete Casas, Loures, Portugal, 2674-506 (FEI#3002807208). There is a U.S. affiliate of Hovione – Hovione LLC, 40 Lake Drive, East Windsor, New Jersey 08520. Other Hovione sites are located in: China (a joint venture with Hysin), Ireland (Hovione Ltd), Switzerland (Hovione Inter AG), and sales offices in Hong Kong, Shanghai, and Mumbai.

Hovione Macau is located in a residential area and about 8 miles from the local Macau Airport. The Macau plant was built in 1986. A major expansion was finished in 2001. The plant occupies a land area of around 111000 m². The facility includes administration, QC laboratories, production buildings, warehouse facilities, and utility areas, covering a total area of around 6000 m². Please also refer to the firm's Site master plant **exhibit 4.**

Hovione Macau site has around 130 employees and produces DMF and VMF products as explained below.

Product Name	**Doxycycline Hyclate**	**Doxycycline Monohydrate**	**Ivermectin**	[redacted]
Years product has been produced by the firm	26 years	23 years	16 years	14 years
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health Condition considered for product	An antibiotic used to treat bacterial infections including those that cause acne, treats certain skin condition like rosacea.	An antibiotic used to treat bacterial infections. It works by slowing the growth of bacteria	A broad-spectrum antiparisitic. Used in humans in the treatment for example of onchocerciasis.	Veterinary, [redacted]

HM sales volume in fiscal year 2012 was 70 tons of all product combined. Sales to North America represented about 60% and Europe 25% and the rest to Australia/New Zealand.

Attached, as **Exhibit 1**, is Hovione's onset presentation. The presentation includes information about:

- Hovione manufacturing sites worldwide.
- APIs associated with USA filed applications.
- An aerial photo of the Hovione, Macau plant.
- A layout of the Hovione plant floor diagram.
- History of the Hovione, Macau plant (also provided below).
- Number of employees at the Macau plant.
- Organizational chart of the Macau plant.
- List of FDA inspections conducted at the Macau Plant.
- Photos of equipment at the Macau plant.
- Flow process for products produced at the Macau Plant.
- Quality System information and philosophy.

The Key responsible persons for the day-to-day operations of the Macau site are:

Mr. Eddy Leong, General Manager
Mrs. Rainbow Chung, QA Head
Mrs. Jenny Fong, QC Head
Mr. Jonny Cheong, Production Director
Mr. Daniel Mok, Industrial Engineering Head
Mr. Man Kit Chan, Processing Order Head
Mr. Paul Kuong, Financial and Administration Director

Exhibit 2 is Hovione, Macau Plant organizational chart listing Mr. Eddy Leong as General Manager. Mr. Leong reports to Mr. Jorge Pastilla, General Manager, Technical Operations (Asia). Mrs. Rainbow Chung is the Quality Assurance Head and she reports to Mr. Jose Lisboa, Corporate QA Director.

The firm is registered with FDA. The firm is in operation 24/7 for production and QC. Production slows down during August and Chinese New Year. Maintenance is performed when production is less generally during August.

The web address is http://www.hovione.com. As related, a synopsis on the history of Hovione, Macau Plant follows.

1959: Hovione was founded
1986: Factory in Macau – China was constructed
1987: Macau plant approved by US FDA
2001: Double of production capacity in Macau
2005: ISO 14001 Certification in Macau
2010: OHSAS 18001 Certification in Macau

INTERSTATE COMMERCE / JURISDICTION

The Hovione Macau plant produces APIs that are exported and marketed in the USA. **Exhibit 5** is a complete list of lots and quantities shipped to the USA for use in connection with USA filed [redacted]. The firm's sales catalog describing the services provided and generic API products produced is included as **Exhibit 3.** [redacted] Consequently, these actives produced by the Macau plant and exported to the USA are considered drugs by definition in the FD and C Act.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

At the Onset of the inspection, I displayed my official credentials to Mr. Eddy Leong, General Manager, as well as other responsible personnel for Hovione including Ms. Rainbow Chung, QA Head, Mr. José Lisboa, Corporate QA Director, and Ms. Luisa Paulo, Compliance Director. These individuals were present during the entire inspection and provided information for this report. As reported, the individuals responsible for Hovione Macau plant are:

Mr. Eddy Leong is the site General Manager. His scope of responsibilities include:

- Company operations in Macau.
- Promoting awareness of customer requirements and statutory, regulatory and legal requests;
- Business performance evaluation.
- Periodic reviews of the Quality Management System and of the Environmental Management System.
- Proposing necessary investments in order to fulfil the established objectives and stimulate new technological and management developments.

Mrs. Rainbow Chung is the Head of QA. Ms. Chung reports administratively to Mr. Leong, but on quality assurance related issues to Mr. Jose Lisboa. Her scopes of 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.

Mrs. Jenny Fong is the head of QC. Ms. Fong reports to Mr. Leong. Her scopes of responsibilities include:

- cGMP compliance requirement in QC laboratory operations and also compliance with Safety, Environmental and Health Regulations.
- Supervising QC Laboratory operations and ensuring analytical work is performed as per approved methodology and meets customer's satisfaction and company established objectives.
- Ensuring training of QC personnel.
- Ensuring equipment is qualified, calibrated, and maintained as per written procedures.

Mr. Johnny Cheong is the production director. Mr. Cheong reports to Mr. Leong. His scopes of responsibilities include:

- Assuring customer orders are filled as per agreed production schedule.
- Minimizing production costs by assuring process yields are met and processing operations are carried out in an efficient manner.
- Global overviews of operations, aiming to assure that the company policies are duty followed.

Mr. Antonio Cotao is the Head of Product Warehousing. His scope of responsibilities include: ensuring raw materials and finished products are properly stored and controlled, providing required material quantities to customers, and assuring shipments are prepared according the established schedule.

Ms. Graça Mata is the regulatory affairs director for Hovione. She was not present during the inspection. She handles all regulatory matters dealing with filed the master files. She is stationed in Portugal.

Exhibit 2 is the Hovione Macau's site organizational chart. Records were in English and all employees of the plant I met spoke English well.

For future inspections the assigned FDA contact persons are:

Mr. Eddy Leong, General Manager
Hovione PharmaScience Limited
Estrada Coronel Nicolau de Mesquita, Taipa, Macau
Tel: (853)88934119

Fax: (853) 28827714
Email:eleong@hovione.com

Mrs. Rainbow Chung, Head of QA
Hovione PharmaScience Limited
Estrada Coronel Nicolau de Mesquita, Taipa, Macau
Tel: (853)88934154
Fax: (853) 28827714
Email:rchung@hovione.com

The US regulatory agents for products produced intended for the US Market are:

US Agent	Products sold /Exported	Name of Customer/Broker/or importer
Hovione LLC 40 Lake Drive East Windsor, NJ 08520 U.S.A. Representative: Ms. Dirce Macário Head of Quality Assurance dmacario@hovione.com TEL: (+1) 609 918 2448 FAX: (+1) 6099182615 or Ms. Carla Vozone Business Development Director cvozone@hovione.com TEL: (+1) 609 918 2466 Fax (+1) 6099182615	Doxycycline Hyclate Doxycycline Monohydrate/ Doxycycline Monohydrate (micronized) Ivermectin	Hovione LLC 40 Lake Drive East Windsor, NJ 08520 U.S.A.
[redacted]	[redacted]	[redacted]

Post-inspectional correspondence (as per FMD-145) should be sent to:
Mr. Eddy Leong, General Manager
Hovione PharmaScience Limited
Estrada Coronel Nicolau de Mesquita, Taipa, Macau
Tel: (853)88934119
Fax: (853) 28827714

FIRM'S TRAINING PROGRAM
Most production personnel and QC analysts have been with the firm for more than 10 years. Training to operators and QC analyst is provided on the job. As reported, education and tenure with Hovione for some Key personnel follows:

Mr. Eddy Leong, Chemical Engineer, joined Hovione in 1997.
Mrs. Rainbow Chung, Chemical Engineer, Graduated from Berkeley University, California joined Hovione 10 years ago and has been QA Head since 2006.
Mr. Jonny Cheong, Chemical Engineer, joined Hovione in 2006.

Routine training is provided annually based on a written plan. Each department is responsible for developing a training plan for their department employees. A GMP exam is given annually. 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.

MANUFACTURING/DESIGN OPERATIONS

Quality System: Hovione is a global company with an established global quality structure. Mr. Jose Lisboa is the Corporate QA Director and Mrs. Paulo is the Corporate Compliance Director. Both Mr. Lisboa and Mrs. Paulo have been with Hovione for over 30 years. Mrs. Chung is the Head of QA at the Macau Facility and Mrs. Fong is the Head of QC.

The QA key functions include:

- Documentation Control.
- Final Product Release – review BPR and related analytical results
- Training – procedures, GMP related.
- Deviations – CAPA.
- Change Control – changes that may have GMP impact.
- Audits.
- RM manufacturer's audits.
- Internal audits.
- External audits (customers, authorities, etc.).
- Product Quality Review.
- Quality Complaints – coordinate the investigation & CAPA.
- Stability studies (Long term & accelerated conditions).
- Environmental monitoring (Water control & Air Monitoring).
- Validation (Process and cleaning).
- Equipment qualification, calibration, and preventive maintenance.

The QC Key functions include:

- Managing all cGMP activities within the Quality Control (QC) laboratory in accordance with all applicable regulations and procedures
- Analyzing and releasing of all materials used for manufacturing.
- Conducting environmental testing (air particulate counting, microbial air testing, and water analyses).
- Supplier Approval and evaluating quality of new suppliers.
- Analytical equipment qualification (DQ, IQ, OQ and PQ) and routine calibration.
- Analytical Method Development, Validation and Inter-laboratories Transfer.
- Managing stability studies.
- Internal standards calibration.
- Updating product specifications as per regulations and clients' request.
- Managing retained samples.

Some of the Key written procedures for the firm's Quality Unit are:

Document Title	Document Number	Effective Date on HM (Year/Month/Day)
Document control and procedure format	HQ.CCO.COP001.5.EP	2013.01.23
COP, SOP and IOP structure	HQ.CCO.COP001-A3.0.EN	2006.09.22
Hovione mission and major policies	HQ.CCO.COP002.2.EN	2010.04.07
	HM.CCO.COP002.2.CN	2010.04.07
Quality Management Responsibilities	HQ.CCO.COP003.1.EN	2008.03.26
Management Review	HQ.CCO.COP004.1.EN	2007.03.02
Quality/HSE Management – Internal and External Auditing	HQ.CCO.COP005.2.EN	2012.07.23
Quality Management – Product Quality Review	HQ.CCO.COP006.1.EN	2006.12.13
Training	HE.CCO.COP007.3.EN	2012.07.23
Building, facilities and utilities	HQ.CCO.COP008.2.EN	2011.02.17
Electronic records and electronic signatures	HQ.CCO.COP011.1.EN	2008.07.31
Specifications	NJ.CCO.COP012.3.EN	2013.01.17
Manufacturing Process Documentation	HQ.CCO.COP013.3.EN	2011.03.09
OOS Investigation / Investigação de resultados OOS	HQ.CCO.COP015.5.EP	2012.07.30
Reception and Storage of Products	HQ.CCO.COP016.0.EN	2004.03.23
Quality Control of Products	HE.CCO.COP017.3.EN	2012.09.19
Re-evaluation and expiry dates for products	HQ.CCO.COP020.0.EN	2004.03.25
Packaging and Identification Labeling	HQ.CCO.COP021.1.EN	2006.02.13
Distribution of Products	HQ.CCO.COP022.3.EN	2013.01.17
Certificate of Analysis	HQ.CCO.COP023.0.EN	2004.03.04
Stability	HQ.CCO.COP024.4.EN	2010.07.16
Validation	HQ.CCO.COP025.3.EN	2011.02.17
Cleaning verification and validation	HQ.CCO.COP026.5.EN	2009.06.15
Change Control	HQ.CCO.COP027.5.EN	2011.03.16
Reprocessing, reworking and returned products	HQ.CCO.COP028.0.EN	2004.05.24
Handling of complaints	HQ.CCO.COP029.3.EN	2011.04.13
Product Recall	HQ.CCO.COP030.1.EN	2011.03.09
Equipment Qualification	HQ.CCO.COP036.1.EN	2006.08.25
Analytical methods validation	HQ.CCO.COP037.2.EN	2009.06.10
Computerized systems validation	HQ.CCO.COP039.2.EN	2012.07.23
Regulatory Inspections and Customer Audits	HQ.CCO.COP042.2.EN	2012.05.21
Risk Management	HQ.CCO.COP047.0.EN	2013.01.17
Backup and restore procedure	HQ.CCO.COP048.0.EN	2013.01.23

Master Batch Production Record (MBPR) control: A copy of the master BPR is kept under lock and key in production. The production secretary makes copies using the master BPR and records copies made and issued. She stamps the BPR with the lot #.

Annual Product Reviews (APRs): The firm has written procedures for conducting quality product reviews. The requirements for the APR are defined in SOP Q.CCO.COP006.1.EN. The APR SOP requires, but is not limited to the following:

- Review all APIs produced at the Macau plant
- Review of process deviations, analytical test deviations, and yields
- Review of complaints, product returns, and recalls.
- Review of stability test results
- Review of OOS and corrective and preventive actions.
- Review of changes (manufacturing and analytical).
- Review of validation including process, analytical, and cleaning.
- Summary results of the annual evaluation

The APR SOP requires the review to be done annually. The reporting period covers production from April to March. I reviewed the 2011 and 2010 APR reports for Doxycycline Monohydrate (Internal Code 05MA64U) and Doxycycline Hyclate (Internal code: 05MA51U). Based on the 2011/2010 APR reports, in 2010/11:

Item reviewed	Product Internal Code	2010	2011
Number of batches produced	05MA51U	78	87
	05MA64U	20	26
Rejected batches	05MA51U	3	12
	05MA64U	1	3
Batches reprocessed	05MA51U	3	13
	05MA64U	1	2
Batches reworked	05MA51U	0	0
	05MA64U	0	0
Batches returned	05MA51U	1	18
	05MA64U	0	0
Complaints	05MA51U	3	0
	05MA64U	1	1
OOS results	05MA51U	2 (Reason: Product Description)	2 (Reason: Product Description)
	05MA64U	2 (Reason: Bulk Density)	3 (Reason: [redacted] contents)
Stability Failures	05MA51U	None. The product is stable	None

		for 60 months (retest period)	
	05MA64U	None The product is stable for 24 (retest period) months	None
Recall	05MA51U and 05MA64U	None	None

Complaints: I asked the firm to provide a list of Complaints that had been received by the firm in the past three years. I reviewed the APR reports to assure complaints that had been received by the firm were also included in the APR report. There were eight complaints registered between 10/15/2010 and 7/5/2012. Two of the complaints (Event #s. 7052 and 7538) were received from claiming that a broken tie-tag was found in two drums and a piece of a 2-inch tie-tag was found in between two PE bags in one drum. Generally, the complaints are reported to the firm via email. I did not review these two complaints, but reviewed the other six complaints mentioned below.

Complaint No. 01-2010, (Event no. 6734): Doxycycline Hyclate, Batch #05MA51U.HM This complaint was filed by on 10/15/2010. The firm received an email from . The reason for the complaint was: was found out of the limit). This investigation was completed and closed by QA on 5/24/11. This batch was returned to the firm.

Complaint No. 02/2010, (Event no. 7051) Doxycycline Hyclate, Batch # 05MA51U.HM: This complaint was filed by on 11/8/10. The reason was: was found out of the limit on specification. This investigation was complete and closed. This batch was returned to the firm.

Please note that the two aforementioned complaints are similar. Initially the firm's specification for was This was the specification that was in effect when the two aforementioned batches were shipped to the USA. It was reported that there is no USP requirement for However, an FDA reviewer requested the level of this impurity be The specification was changed to The clients were informed by email after the specification change was made. The firm's client tested the API after the specification change was made and found that the impurity in these lots was higher than Hovione tested the retain sample and client's provided samples and found that the impurity was under the initial specification of . However, since there was a new set specification of the product was returned back to Hovione.

Additional stability studies to evaluate the impurity: The product is packed for commercial sale in 50 kg size containers. Initially, stability studies were performed using two gram samples. Based on complaints received claiming the impurity was higher than , the firm conducted an investigation and theorized that perhaps the sample size used of 2 grams was not representative of the commercial package size for the product. Consequently, the firm increased the

sample size for stability studies to 500 grams. They felt the 500 gram sample size was more realistic to represent the 50 kg commercial size package. It was reported that the increase of the sample size for stability study was necessary because the volume of [redacted] could increase based on the quantity of product since there was [redacted] in the product. It appears that over time the [redacted] would react with [redacted]. So the higher the quantity of the product, the more likely the [redacted] impurity could increase. The firm reported that the key to reducing the [redacted] in the finished product is to have less [redacted] available in the product thus reducing the impurity of [redacted] in the finished API. Based on the current process, the firm is able to maintain the [redacted] impurity at around [redacted]

Reviewed data included: (Complaints 01/2010 and 02/2010):

- Complaint Investigation reports.
- Retain sample log book #3 for MA51 documenting samples were pulled for testing on 10/7/2010. Initial correspondence on complaints received on 10/1/2010.
- Analytical test record #268.
- Raw data (GC) related to the testing of the retention sample, client sample as result of Complaint # 01/2010, Analysis date of October 8, 2010.
- Raw data (GC) related to the re-test of previous batches as result of Complaint # 01/2010. Analysis date of October 20, 2010.
- 05MA51 (Doxycycline Hyclate): Determination of [redacted] by GC-HS document # HM.CR.GC3949-HM-FP1.2.EN., dated 10/26/2011.
- Documentation from World Courier documenting that samples sent to Hovione were in cold conditions (Complaints: 01/2010 and 02/2010).
- Copy of letter to FDA regarding the proposed revision of the Doxycycline Hyclate (DMF 13714) specification to widen the limits for the [redacted] impurity and store the product under [redacted] conditions (**Exhibit 11.**

Complaint No. 15706, Doxycycline Monohydrate, Batch #05MA64U.HM[redacted] Reason for complaint: OOS on related substances by HPLC (any other impurity) during the analysis of the batch by client. The complaint was filed by [redacted] on 2/13/2012. This batch was returned to the firm. Hovione tested the retained sample and confirmed that the product was in specification. Hovione tested the product based on the client's test method and found no difference and that the product met specifications. Based on Hovione's experience, aberrant results could occur if the standard solutions, during sample preparations, are not handled correctly. It is recommended to be very careful during preparation of the solutions. It could be suspected that the firm's client results might have something to do with how the standard solutions were prepared. The finished API was returned to Hovione based entirely on a commercial decision to maintain good business relations with the client and was not due to the product. The complaint was closed by QA on 5/30/2012.

Reviewed data included:

- Complaint investigation report.

- Retain sample Log-book #2 for MA64. The sample log book documented that the sample was pulled for testing on 2/13/12.
- Record for balance # BL10-c. This is the balance used to weigh the sample tested.
- Chromatography logbook for apparatus used #LC4.11.
- Analytical raw data for sample of finished batch and retain sample tested after complaint was received. Also, analytical method used for testing product and retain sample document # CRLC-066-HM-FP1 initial test done on 12/19/2011. Procedures followed for performing the initial test and the re-test after the complaints were similar.

Complaint No. 16549, Ivermectin Batch #s: 05KB21.HM[redacted] and 05KB21.HM[redacted] [redacted] on 3/22/2012. The reason for the complaint was: OOS on any other individual impurity (NMT 0.5%). This investigation was completed and closed. This batch was returned to the firm.

Complaint No. 16885, Ivermectin Batch #: 05KB21.HM[redacted]: [redacted] filed complaint on 3/30/2012. The reason for the complaint was: OOS of any other individual impurity peak. This investigation was completed and closed.

The firm's investigation determined that the complaints were attributed to a particular brand of column used. It was found that the Thermo Scientific column can't show the [redacted] peak whereas the YMC column would. Some of these lots had been shipped to Europe. Only a few lots had been shipped to the USA. The only lot that was kept in the USA was lot HM[redacted], reportedly kept for use in product development only.

When complaint No. 16549 was received Hovione was using four different serial number columns from Thermo Scientific. Hovione initiated an investigation to find the root cause for the complaint. The firm purchased two additional columns from Thermo Scientific. When testing the product using the new columns it was found that the columns produced non-uniform peaks of different shapes. The firm then purchased columns from YMC and found that they were able to detect the [redacted] peak using the YMC chromatographic columns. With the YMC columns the peaks were sharp as expected. The firm then tested all lots that had been tested using the Thermo Columns using the YMC column. Since this complaint incident, Hovione now spikes the sample at 2% to make sure the column would detect the [redacted] peak. This is normal procedure followed during routine testing. The [redacted] is coming from the process [redacted] when hydrogenation occurs. An in-process test for [redacted] is performed to assure it has been [redacted] removed.

Reviewed data included: (Complaints 16885 and 16549). These complaints are related.

- Complaint investigation reports.
- Usage logbook for Thermo Scientific chromatographic columns #281 and 265. The firm tracks all chromatographic columns used.
- Usage logbook #191.3 for YMC chromatographic column used in the investigation of complaint # 16549. The first lot tested with this column was HM00040 on 3/14/12.
- Retain sample log documenting that samples were pulled for testing on 2/13/2012.

- Method for testing product to determine specific chromatographic columns used.
- Records for spike sample test.
- Analytical data for the retesting of retain samples using to the YMC chromatographic column after complaint was received. Analytical data related with investigation performed includes the chromatograms of previous batches supplied to the same client (batches HM[redacted] up to HM[redacted] plus batch 1 and 6 and V0101); all different columns in stock in the lab with the same packing type (Thermo Scientific and YMC), retention sample of the complaint batch and client sample; stability batch data of batch HM[redacted].
- Usage logbook for chromatography apparatus # LC10.2.
- Master batch production record to verify the change of Oxidation step to require testing for the[redacted]
- Stability test results for lot HM[redacted] at 3 months at 25°C/ 60 % RH using the YMC column.
- SAP record for determining accountability and distribution of these two lots.

Complaint No. 18761, Doxycycline Hyclate, Batch #s: 05MA51-HM[redacted] and 05MA51-HM00[redacted]: The complaint was filed by [redacted] on 7/5/2012. The reason for the complaint was: OOS on [redacted]. This complaint was closed by QA on 10/23/2012. This batch was returned to the firm. This complaint claimed the product was near specification. The client found the [redacted] level was approaching specification of [redacted] Hovione also tested the product based on client's method. Hovione initial test result was [redacted] and the retain sample was [redacted] Hovione also tested the sample provided by the client and found [redacted].

Reviewed data included:

- [redacted] (client ref method) client analytical and old method used before the complaint.
- Raw data related to retain sample, client sample, and spike sample tested.
- Analytical test data for Batch # 05MA51U.HM[redacted], Analysis date of July 27, 2012.
- Sample receipt documenting samples were received from the client were kept refrigerated during shipment.

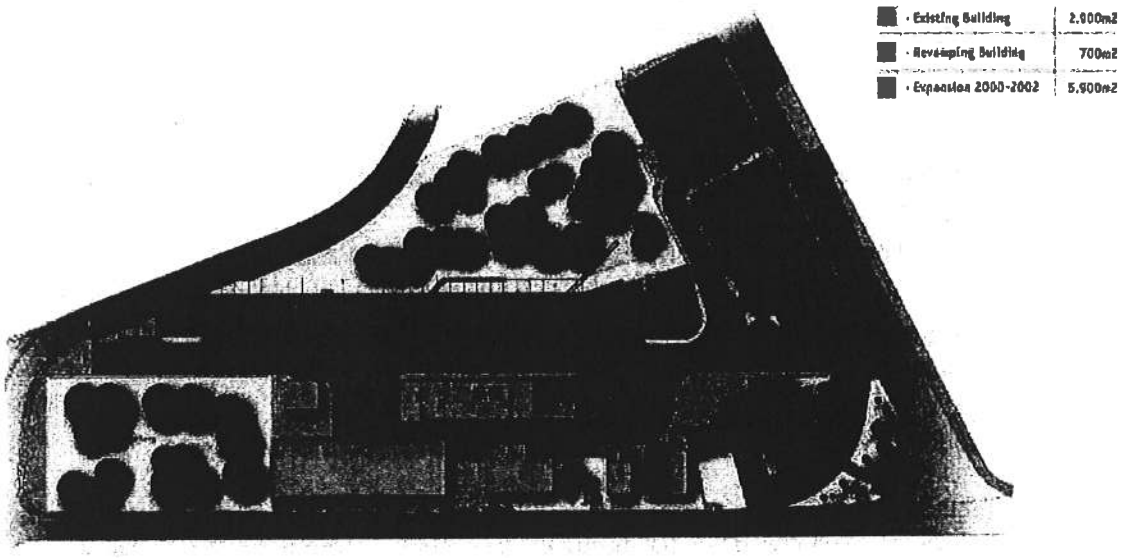
No issues were found with how the firm documented and investigated complaints.

Returns: I requested the firm to prepare a list of all lots that had been returned to the firm in the past two years (**Exhibit 7**). I reviewed this list during the inspection. There were 28 lots that were returned due to various reasons. They include: Business decision, for further processing to achieve tighter specifications, [redacted] out of client's requirement, OOS on any other individual impurity, and OOS on[redacted] The Annual Product Review report included an evaluation of returned batches. I reviewed the firm's documented investigation reports into returned products that related to the OOSs (please refer to explanation into complaint numbers 16549 and 18761 above). No issues were found.

The firm has a Site Master File (SMF), **Exhibit 4**. The SMF includes information but is not limited to:

- Personnel.
- Quality Policy and a description of the quality management.
- Qualification and calibration of equipment
- Documentation.
- Production Operations.
- Validation Policy.
- Distribution, Complaints, and Product recall.
- Organizational chart.
- Process Description for products produced
- Self-inspection, etc.

Description of Plant and Equipment: Diagram showing the layout of the plant:



The buildings that comprise the facility include:

Building 1 or BK1: (Administrative offices and the QC laboratory (located on level 3) and warehouse).

Building 3 0r KK3: Hydrogenation for the Doxycycline intermediate. Equipment Hydrogenator: H3001.

Building 2 or BK2: Production of Doxycycline Hyclate, Doxycycline Monohydrate, Ivermectin, [redacted]; Softened water system located here. Equipment: Reactors: RV1201, RV2001, RV4002, RV5001, RV5004, RV6003, RH6001; Centrifuges: C201, C301, C302; and Dryers: VTD, A431, BI1601.

Building BK2A (next to the yellow color section of building 2 but in Red [redacted] Production Expansion was commissioned at the end of 2001. Equipment: **BK2A** include: Reactors: RV4003, RH6002, RV10001, RH4001, RV6001, RV10002; Centrifuges: C401, C402; and Dryers: BI4001, PD1201.

Dedicated equipment for product and processing steps:

Ivermectin: hydrogenation and drying is dedicated; reaction and filtration is dedicated since 2010 year.

Doxycycline Hyclate and Monohydrate: reaction, filtration and drying are dedicated since 2009.

Doxycycline Intermediate: hydrogenation and drying dedicated.

Multipurpose equipment:

Doxycycline Intermediate: Steps after hydrogenation, and filtration

[redacted]: equipment used is multipurpose

Process controls: I reviewed batch production records, process deviations, process flow, changes, spoke with production personnel during my reviewed of changes, and review new equipment qualification (Reactor RV5004).

Changes: I requested the firm to prepare a list of all major changes that occurred in the past two years (**Exhibit 8**). I reviewed this list during the inspection. There were three changes related to the Doxycycline Hyclate and Doxycycline Monohydrate process. They included:

- Change 3722: Installation of new reactor RV5004 to replace RV4001 in MA production line and to be qualified for the same steps performed on RV5004. I reviewed this change during the inspection. Reduction of [redacted] in MA62 process no. 3. (Validation was on-going and not yet completed);
- Upgrading of Packing Room 4 to increase the flexibility and productivity.

There was one change related to the production of Ivermectin. New manufacturing technique (MT) and master batch production record (MBPR) for the reprocessing steps of 05KB21. This process was validated.

There were two changes related to the [redacted] process. These were:

- Change #3363: Qualification of alternative supplier for [redacted]
- Qualification of alternative supplier for [redacted]

Related to Change #3722, I reviewed the listed documents:

- Change stream (Change request) # 3722 for performing this change. QA approved this change and performed an assessment the change may have on the validated process.
- Batch production records for the last batch produced using reactor RV4001, Batch # HM00297 and the first batch produced after the new reactor was installed and qualified; batch # HM00301.
- Technical data dated 2/20/86 for the design of the glass lined reactor RV4001 (old reactor) and how it compared to newly installed GL reactor RV5004 dated 8/28/10.
- Operation qualification Protocol for the glass lined reactor RV5004, document # HM.QSP.EQ142.O.EN dated 9/8/2010. The parameters checked were temperature and speed. The reactor was also tested for leaks.
- Usage logbook for reactor RV5004. The usage log book documented that the reactor was cleaned on 9/10/2010 after it was installed and qualified. The reactor was used initially on 9/11/2010.
- Cleaning record document # CV/10-043 Rev. 00. This was the cleaning procedure performed.
- Routine cleaning document #HM-PR-10P400-A1-5-EN for cleaning done on 9/12/2010.

Related to Change #3363, I discussed the firm's procedures for qualifying vendors and raw materials. The following was learned.

1. The purchasing department identifies a potential material supplier.
2. Purchasing determines if they have ever received samples from the potential supplier.
3. Purchasing sends to the potential supplier a questionnaire called 'Vendors Data Form.' The potential vendor must report whether they have a GMP certificate and commit to report major changes, etc.
4. The suppliers must have cleaning and cross contamination procedures.
5. The firm makes a request to the potential supplier to send samples for QC testing and specification development.
6. The Macau facility performs an experiment with the product (Produce a small scale size batch) to determine if the material will be suitable for commercial batching.
7. Purchasing writes a proposal for purchasing material for process validation.
8. QA does a temporary approval of the product to give purchasing authorization to purchase the material.

9. Purchasing buys enough quantity of the product for use to produce validation batches.
10. Validation batches are produced as in the case associated with change order #3363. The three batches produced were: HM[redacted], HM[redacted], and HM[redacted]. These batches were placed on stability.
11. If everything is acceptable QA approves the vendor.
12. The firm also performs a physical audit of the supplier. On 9/4/2010, Hovione [redacted] visited [redacted]

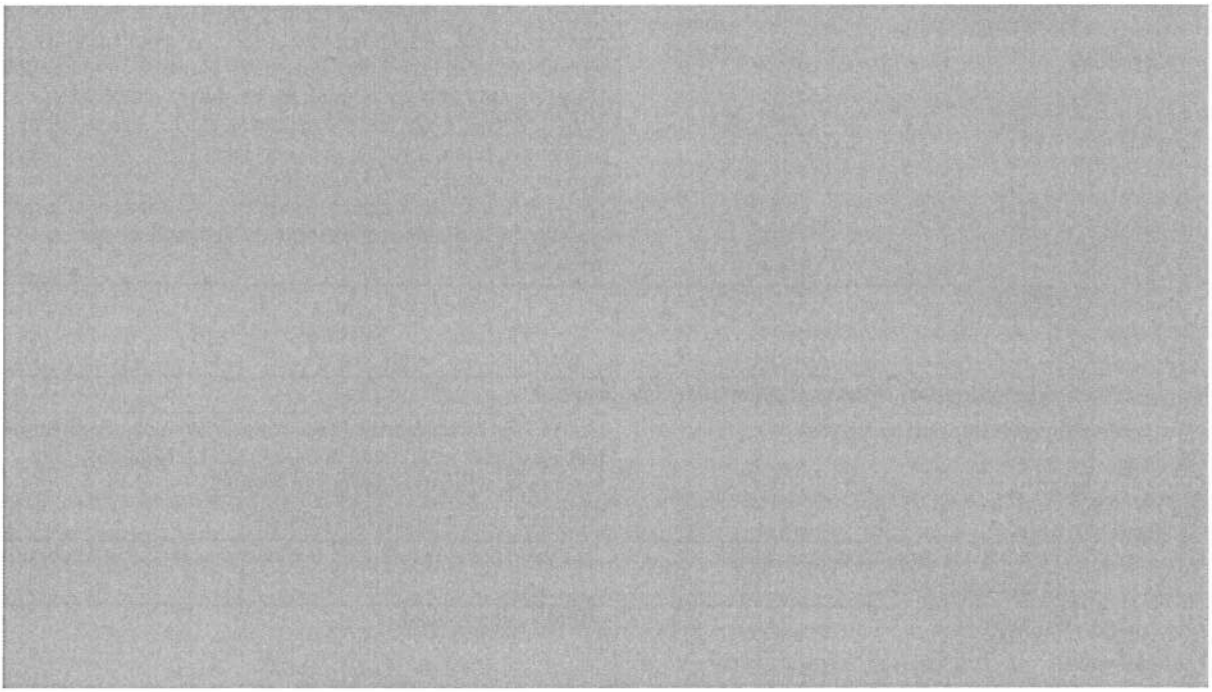
Process Deviations: I asked the firm to provide a list of process deviations that had been documented and investigated in the past two years (**Exhibit 9**). Process deviations were identified, documented, and investigated. I reviewed the APR reports to assure deviations that had occurred and investigated were also included in the APR report. The table below summarizes the documented deviations for API products produced.

Product	**Number of deviations**	**Classification of Deviations**
Doxycycline Hyclate and Doxycycline Monohydrate	7	All were classified as non-critical.
Ivermectin batch #05KB21 HM[redacted]	1 Event #16373	Non-critical. Extra crystallization. I reviewed this manufacturing deviation. It was found that the impurity H at the in-process step was higher than normal, but was in spec. A sample is taken of the wet cake and tested for the impurity H (step 455 in the BPR). If the impurity H is not normal, the product is dissolved in [redacted] and recrystallized again. As a result of having the impurity higher than normal, [redacted] step was performed. Normally, [redacted] steps are performed. The batch production record documents that [redacted] step was performed. The product met specification.
[redacted]	Zero	
Deviations related to the production of the Intermediate		
Doxycycline Intermediate	21	One (#5703) was classified as a critical deviation. (Brownish-black particles were found in IN-04MA62.HM[redacted] The product was dissolved again and filtered. All other were non-critical deviations.
There were several documented deviations due to the yield being out of limit, but there was no quality impact to the finished product.		
Ivermectin	3	All were non-critical.
[redacted]	1	Non-critical

The Critical Process Parameters for Doxycycline Hyclate and Doxycycline Monohydrate are:

Processing Stage	Parameter	Specification
Doxycycline Intermediate (Doxycycline p-Toluenesulphonate)		
Hydrogenation		
Doxycycline Hyclate		
Filtration		
Doxycycline Monohydrate		
Product Suspension		
Crystallization		

The process flow for **Doxycycline Hyclate** is:



[redacted]

I requested the firm to provide a list of batches that have been produced, released, and exported to the US in the past two years. I reviewed the process flow for producing the API along with the batch production records for the listed batches. I reviewed the batch production records for listed batches. No problems were found.

Doxycycline Hyclate API
05MA51U.HM[redacted]
05MA51U.HM[redacted]
05MA51U.HM[redacted]
05MA51U.HM[redacted]
05MA51U.HM[redacted]
05MA51U.HM[redacted]

Ivermectin API from the [redacted] step forward.
05KB01-HM[redacted]
05KB01-HM[redacted]

Raw Material Control: I reviewed procedures for receiving, inspecting and sampling raw material. I reviewed procedures for qualification of raw material suppliers. I reviewed testing and specifications of raw materials including solvent recovery and use. I inspected raw materials and finished product storage areas including rejected product areas.

Qualification of Raw Material Suppliers and RM testing: *As explained previously in this report, the firm has procedures for* the qualification of raw material vendors. For new added vendors of starting raw materials, the vendor and sample for the starting RM are evaluated. The firm then puts a lot produced with the new starting raw material on stability study. I inspected raw material and finished product storage facilities. I inspected the tank farm for solvents used. The storage areas were well maintained. All containers were identified. Some raw materials and finished product required to be stored refrigerated. No problems were found.

I reviewed the receiving, sampling, and testing procedures for raw materials. I selected documents for Ethanol stored in tank # T002 for shipments received on 12/31/11 and 1/5/2012 and used to produce batch [redacted]. Mr. Antonio explained the procedures for receiving solvents as follows:

1. Documentation accompanying the raw material from the vendor is reviewed.
2. The RM is entered in SAP.
3. A hose is used to sample the tank. This is performed by QC.
4. QC tests the product based on written specifications.
5. QC approves the product in LIMS that communicated with the SAP system.
6. A dedicated hose is used to transfer the product from the truck to the holding tank once product is found ok by QC.
7. All solvent arrived in dedicated tanks and the suppliers are checked to assure the tanks are cleaned.
8. Each holding tank with solvent in it is identified. Each transfer pipe to the plant and equipment are identified. Solvents can be transferred from the holding tank to a drum, which is brought into the plant.
9. The tank is tested every 3 months.

I found no problems with raw material controls including sampling, labeling, storage, testing, use, and accountability.

Recovered solvents: Any recovered solvent is used after it has been tested to comply with written specifications. The recovered solvent is used to produce the intermediate. Sampling of the distilled

recovered solvent is performed every 24 hours by GC (IPC testing). QC tests the product in the tank after it is full and releases it for use to produce the intermediate only.

Laboratory controls: I reviewed OOS events and laboratory deviations, checked the qualification of a newly installed FTIR, reviewed usage logs for equipment, and reviewed analytical data for batch numbers: 05MA51U.[redacted], 05MA51U.[redacted], 05MA51U.[redacted], 05MA51U.[redacted], 05MA51U.[redacted], 05MA51U.[redacted], 05KB01-[redacted], and 05KB01-[redacted] The laboratory was in operation during the inspection and equipment observed in the laboratory was normal. Analyst recorded information contemporaneously with testing being performed. The laboratory maintains a log book on chromatographic columns, standards, and instruments. The batches are released after the analytical testing is double checked including a final review by QA. No issues were found in the laboratory.

OOS Events: I asked the firm to provide a list of OOS events that had been documented and investigated in the past two years. There were seven OOS reports related to out of specification for residual solvent[redacted] particle size, and description (black particles). Three of the OOS were attributed to human error, one was due to an unclear procedure, and three initially classified as OOS on particle size were classified as non-cause after the investigation determined they were actual OOS. I reviewed the OOS for Doxycycline Hyclate mentioned below. Doxycycline Hyclate can be used to produce Doxycycline Monohydrate. In this case the OOSs were attributed to [redacted] contents, particle size, and black specks so the product can be reprocessed or used to produce Doxycycline Monohydrate.

OOS no. & Date	OOS Batch	Quantity (Kg)	Obtained Batch after OOS	Quantity (Kg)	Deviation no.	Reason for failure
OOS/011-140 7/4/2011	Doxycycline Hyclate 05MA51U.[redacted]	[redacted]	05MA64U.[redacted]	[redacted]	11045	Residual solvent[redacted] OOS: It was found that after the replacement of a gauge (CL15), the operators and supervisors were not trained to use the new gauge with different settings and controls. They have difficulties in reading and setting the correct amount to be washed. Since the collection of all solvent quantities was carried out prior to the filtration, total quantities were matching that stated in the BPR. However, without knowledge on controlling the setting, the equal distribution of washing between parts could not be guaranteed and could subsequently result in [redacted] failure. The OOS
OOS/011-141 7/4/2011	05MA51U.[redacted]	[redacted]	05MA64U.[redacted] 05MA64U.[redacted] 05MA51U.[redacted]	[redacted]	11045	

OOS no. & Date	OOS Batch	Quantity (Kg)	Obtained Batch after OOS	Quantity (Kg)	Deviation no.	Reason for failure
						observation could be attributed to the several filtration parts, more could be charged during the washing. With the same standard of spinning as defined in the BPR, the in excess could had been trapped with the product and eventually lead to the OOS. This was classified as human error due to lack of training. Training was given. This product can be used to produce Doxycycline Monohydrate.
OOS/012-109 5/29/2012	05MA51U. 05MA51U.		05MA51U. 05MA51U. 05MA64U.		18073	Description Black particles: This OOS was classified as Human error. It was found that the root cause was related to the changing of the hose MA025 without informing the superior and the cleaning verification was not done correctly. The operator did not put the Teflon slip over the gasket causing the gasket to break down. The BPR has a requirement to assure the hoses have the Teflon gasket. As stated, the operator did not place the Teflon correctly. . I reviewed the inventory document for hoses used. Hose #Mao25 was first used on 11/15/2008. Equipment maintenance record for Reactor RV5001 to filter FQ45. Batch production record . The product was dissolved and filtered again to remove the particles. The product can be used to produce Doxycycline

OOS no. & Date	OOS Batch	Quantity (Kg)	Obtained Batch after OOS	Quantity (Kg)	Deviation no.	Reason for failure
						monohydrate.

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

Laboratory Deviations: I asked the firm to provide a list of laboratory deviations that had been documented and investigated in the past two years (**Exhibit 10**). Laboratory deviations were identified, documented, and investigated. There were a total of 39 documented laboratory deviations. 37 were documented as non-critical and two were documented as critical.

Deviation #14774: This deviation was described as 'Approved 0103422.HM00020 (C_REAN) without Identification (by IR).' This deviation was classified as equipment malfunction. Initially the raw material was tested. The procedures required re-evaluation of the RM at one year intervals. The RM had not been used. The procedure requires identification by FTIR to be performed before use, but it was not performed because the FTIR apparatus was out of service. The RM is a liquid product. All other tests on the RM were performed except identification by IR. I reviewed the usage log for the FTIR-1A, document # 17629. The usage log documented that the FTIR was placed out of service on 5/9/2012. The equipment was calibrated last on 1/6/2012. I reviewed the documentation IQ/OQ for the new FTIR, installed on 6/5/2012.

The other deviation identified as critical was #21710, had to do with the temperature for Stability Chamber for Accelerated Conditions EH3 that was found to be Out of Limit.

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

impurities and stability studies: These impurities were included in the specifications in 2010. However, at a later time it was noticed that the impurity levels on the bulk packaged product (packed in 50 Kg drums) were different from impurity levels noticed on the stability study samples. The stability study sample was 2 grams. In order to confirm the reason for the discrepancies, Hovione started a new stability study using larger stability samples (500 grams). It was found that the size of the sample placed on stability could impact impurity results. Also, Hovione determined that to maintain the stability of Doxycycline Hyclate, the product must be stored By letter, document #DRC2012/158-MGM/NCH, Hovione notified FDA proposing to widen the specification for the impurities, see **Exhibit 11.**

Packaging and Labeling: As explained, the packaging system used follows:

Primary container (Container used to pack the finished product) Polyethylene bags and Aluminum bag

External container: HDPE drums

Closure method: PE bag is tag-tied (normal plastic tag-tie). The Aluminum bag is heat-sealed. Metal tamper-seal or plastic tag-tie is used to lock the drum.

Doxycycline Hyclate and Monohydrate: 2 tag-tied PE bags + 1 heat-sealed Al bag, inside a HDPE drum

Ivermectin: 1 tag-tied PE bag + 1 heat-sealed Al bag, inside a HDPE drum
[redacted]: 2 tag-tied PE bags + 1 heat-sealed Al bag, inside a HDPE drum

An example of the labels for products exported to the USA is included as **exhibit 6**. A sample of the label used with packaged lot is included with the BPR. The packaging system used for the APIs is satisfactory.

MANUFACTURING CODES
An example of the lot numbering system: batch #: **05MA51U.HM00001**

05 – Represents the finished product.
MA51U – is an alpha-numeric material code, MA51U refers to Doxycycline Hyclate.
HM – represents the site where the batch was produced, or Hovione Macau.
00001 – Is a 5-digit sequential number representing the lot 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
[redacted]
Ivermectin – 05KB21
Ivermectin (Wet) – 04KB21001
[redacted]

COMPLAINTS
The firm has written procedures documenting and investigating complaints. I reviewed complaints that have been received by the firm on APIS produced. Please refer to the 'Manufacturing/Design Operations' section of this report above. All complaints were investigated and were closed. The complaint handling system is satisfactory.

RECALL PROCEDURES
No product recalls have occurred.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE
No FDA-483 was issued.

REFUSALS
No refusals were received during the inspection.

GENERAL DISCUSSION WITH MANAGEMENT
I mentioned to management that the firm was in compliance.

ADDITIONAL INFORMATION
Hotel Accommodations: I stayed at the Holiday Inn in Macau. The plant was about an 30 minute walk from the hotel or 10 minutes by car. The hotel offered many amenities including restaurants and the cost was within allowable perdiem.

SAMPLES COLLECTED
No sample was collected.

VOLUNTARY CORRECTIONS
Previously cited observations were minor and were corrected. The firm submitted a written response to previously cited observations. The current inspection revealed no inspectional observations.

EXHIBITS COLLECTED
1. Hovione's onset presentation, 23 pages.
2. Hovione, Macau Plant organizational chart, 1 page.
3. Firm's sales catalog, 28 pages.
4. Site Master File, 22 pages.
5. Complete list of lots and quantities shipped to the USA, 10 pages.
6. Example of the label for products exported to the USA, 10 pages.
7. List of all lots returned in the past two years, 3 pages.
8. List of all major changes in the past two years, 1 page.
9. List of process deviations documented and investigated in the past two years, 4 pages.

10. List of laboratory deviations documented and investigated in the past two years, 2 pages.
11. Document #DRC2012/158-MGM/NCH, 33 pages.

ATTACHMENTS

1. Information sheet to trip coordinator and CDER, 1 page.

Jose R. Hernandez, Investigator