



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

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Inspection Assessment Branch  
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March 10, 2016

Mr. Arturo Jimenez  
President  
Laboratorios Sophia S.A. de C.V  
Avenida Paseo del Norte No. 5255  
Guadalajara Technology Park  
Zapopan, State of Jalisco 45010  
Mexico

Reference FEI: 1000310459  
Reference Inspection Date(s): August 24-28, 2015  
Establishment Locale: Zapopan, State of Jalisco, Mexico

Dear Mr. Jimenez:

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 the above address or number.

Sincerely,

Concepcion Cruz  
Branch Chief  
Inspection Assessment Branch

Enclosure: EIR

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## SUMMARY OF FINDINGS

Inspection of this sterile OTC drug manufacturer was made pursuant to México Post Surveillance Work Plan for FY 2015 issued by ORA/OMPTO/DMPTI under FACTS assignment #11491024, Operation ID #7693366. The assignment requested to conduct a GMP inspection and evaluate the firm's compliance with the Current Good Manufacturing Practices (CGMP's). Coverage for this EI was given under compliance program 7356.002A, Sterile Drug Process Inspections. Profile class SLQ (sterile liquid) was covered.

This is the first FDA inspection at Laboratorios Sophia S.A. de C.V. and was conducted by personnel from the México City Post during the period August 24 – 28/2015. The EI used the system approach established in accordance with CP 7356.002 selecting

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the Full Inspection option reviewing the Quality, the Facilities, the Production, the Materials, and the Laboratory Controls systems. The inspection disclosed objectionable conditions in the Laboratory Controls system, which were reported on a FDA-483 Inspectional Observations form issued to the firm's General Director at the conclusion of the inspection. The observations included in the FD-483 were:

- Failure to follow written procedures intended to assess the stability characteristics of sterile ophthalmic products, and,
- Failure to test containers and closures for conformity with all written procedures and specifications.

The firm's management committed to respond in writing and implement corrective actions to all the deviations noted during the course of the inspection. No samples were collected and no refusals were made.

This inspection was conducted by the México Post team consisting of Investigator Rafael Nevárez and Regulatory Analyst Ana Patricia Pineda. Regulatory Analyst Ana Patricia Pineda supported the EI during the entire inspection. She is a Locally Engaged Staff (LES) hired by the United States Embassy and assigned to FDA to work in support of FDA activities. All information, including documents collected during this inspection and any translation from local language to English by Regulatory Analyst Pineda that supports the FDA-483 and the Establishment Inspection Report (EIR) was collected in collaboration with the FDA investigator. The EIR was written by Investigator Nevárez (RNN) with the exception of those sections specified as written by Regulatory Analyst Ana Patricia Pineda (APZ).

**LODGING AND ACCOMMODATIONS (RNN)**

We stayed at Westin Guadalajara, located at Avenida Las Rosas 2911 Rinconada del Bosque, Guadalajara, 44530, Tel. 52 (33) 3880 2700 ([www.starwoodhotels.com](http://www.starwoodhotels.com)). This hotel had room rates below the per diem. The hotel is located within a commercial and residential area within Guadalajara metropolitan area, approximately at 30 minute drive from the firm's premises located in Zapopan's industrial area. Temperatures during the summer are around 25 - 30°C during the day and approximately at 20°C at night. The hotel is located at approximately 30 minutes by car from Guadalajara's International Airport. The food and service are good at this hotel. I would recommend this hotel for future Investigators scheduled to perform inspections at the above firm.

**ADMINISTRATIVE DATA**

Inspected firm: Laboratorios Sophia, S.A. De C.V.  
Location: Av. Paseo del Norte No. 5255,

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Guadalajara technology Park  
Zapopan, State of Jalisco,  
Mexico  
Phone: 52 55 5396 – 0537  
FAX:  
Mailing address: Av. Paseo del Norte No. 5255,  
Guadalajara technology Park  
Zapopan, State of Jalisco,  
Mexico  
Website: www.sophia.com.mx  
Dates of inspection: 8/24/2015, 8/25/2015, 8/26/2015, 8/27/2015, 8/28/2015  
Days in the facility: 5  
Participants: Rafael Nevarez Nieves, Investigator

**HISTORY (RNN)**

Laboratorios Sophia S.A. de C.V. is a corporate entity engaged in the manufacture of sterile human OTC ophthalmic and synthetic corticosteroid finished products. The firm's manufacturing facilities are located within an industrial area at Avenida Paseo del Norte 5255 Guadalajara Technology Park, Zapopan, State of Jalisco, 45010. From this portfolio, only OTC ophthalmic drug products have been exported to the US.

The firm started operations in Guadalajara in 1946 as a wholesale distributor of drug products. Slowly the firm began to manufacture its own products until 2008 when the firm's management decided to move their manufacturing operations to their current site in Zapopan, State of Jalisco.

Laboratorios Sophia S.A. de C.V. exports products manufactured at their site to Central and South American, and Caribbean countries. The firm initiated the exportation to the US of sterile ophthalmic OTC products in 2011 with products used to refresh and replenish moisture to eyes such as Manzanilla Sophia 0.1%, and Nazil Ofteno 0.02%. According to the firm's management, Nazil Ofteno 0.02% will no longer be exported to the US due to marketing reasons. They also confirmed that to this effect, they had already submitted to FDA CDER Direct a notification reporting the product's marketing end date as 04/29/2015 (see Exhibit 1). A list of OTC pharmaceutical products lots exported to the US for the years 2011 through 2014 along with the lot number, quantities and date of distribution is attached as Exhibit 2 of this report of investigation.

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The firm's corporate management personnel have oversight of all aspects related to sales, research and development, human resources and manufacturing of products. As of September, 2015, the following personnel heads the firm's corporate operations (see Exhibit 3):

Mr. Arturo Jiménez, President

| Name                  | Title                          |
|-----------------------|--------------------------------|
| Mr. Jorge E. González | Vice President                 |
| Mr. Héctor Hernández  | General International Director |
| Mr. Eleuterio López   | General National Director      |
| Mrs. Karina González  | Assistant Vice President       |

Any correspondence issued to the firm should be sent to Mr. Arturo Jiménez, firm's President to the following address:

**Laboratorios Sophia S.A. de C.V.**

Avenida Paseo del Norte No. 5255  
Guadalajara Technology Park  
Zapopan, State of Jalisco 45010  
Tel. 52 (33) 3001 4200  
[ajimenez@sophia.com.mx](mailto:ajimenez@sophia.com.mx)

Laboratorios Sophia, S.A. de C.V. manufacturing activities are performed five days a week, production and laboratory operations are performed in one shift. At present, the firm's complex employs a total of 581 individuals. According to the firm's management, exportations of finished products represent approximately 35% of the total production, from which 37% correspond to ophthalmic products.

Laboratorios Sophia S.A. de C.V. site is registered with FDA in accordance with section 510 of the FD&C Act under central file number 1000310459. The firm is also subject to inspections from national agencies, such as COFEPRIS (México).

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## **JURISDICTION (RNN)**

Laboratorios Sophia S. A. de C.V. has been engaged in the manufacture and exportation of sterile ophthalmic OTC human drugs to the US. As a drug manufacturer, the firm is subject to the adulteration provisions of section 501(a)(2)(b) of the Act, which requires all drugs to be manufactured in conformance with the current Good Manufacturing Practices (CGMP's) outlined in 21 CFR 210/211.

The firm had distributed OTC manufactured products for the Mexican and the US markets. A list of OTC pharmaceutical products lots exported to the US during the period March, 2011 through February, 2014 along with the quantities and date of distributed is attached as Exhibit 2 of this EIR.

## **INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED (RNN)**

On August 24, 2015, I showed my credentials to Mr. Eleuterio López, General Director, Mr. Carlos Martínez, Operations Director, Mr. José Rubén Tornero, Quality Director, Mr. Rafael Castañeda, Quality Assurance Manager, Mr. Guillermo Balderrama, Human Resources Director, and Mrs. Alicia Morfin, Compliance Manager. Mr. López identified himself as the firm's most responsible individual present at the firm. I also introduced them to Regulatory Analyst Ana Patricia Pineda.

Mr. López made some opening remarks and briefed us about the firm's history and background. Later on, we proceeded to visit the firm's manufacturing facility, including the production areas, warehouse, and the quality control laboratory accompanied with Mr. Castañeda and Mrs. Morfin. Mr. Castañeda and Mrs. Morfin accompanied us during the entire EI and coordinated all activities related to the on-site inspection.

Mr. Eleuterio López is the firm's most responsible individual overseeing all manufacturing activities conducted at the site. Mr. López has the duty, power, responsibility, and authority to prevent, detect, and correct violations. He accepted the FDA-483 Inspectional Observations form issued on August 28, 2015. Examples of his responsibilities were demonstrated by organizational charts, by statements made by firm's employees indicating that Mr. López is one of the firm's most responsible individual, and by directives given to those individuals present during the initial interview and the discussion with management meeting.

Mr. Rafael Castañeda is the firm's Quality Assurance Manager. Mr. Castañeda oversees all quality assurance operations at the firm. He has the duty, and responsibility to

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prevent, detect, and report violations. Examples of his responsibilities were demonstrated by organizational charts, his signature appearing on operational procedures, statements made by employees assuring his responsibilities in quality matters and instructions communicated to employees. Mr. Castañeda reports to Mr. Rubén Tornero, Quality Director. Mr. Castañeda participated during the entire inspection, and attended the initial and closing meetings.

Mrs. Alicia Morfin is the firm's Compliance Manager. She is responsible for the firm's regulatory and compliance matters. Examples of her responsibilities were demonstrated by organizational charts and instructions imparted to employees. Mrs. Morfin reports to Mr. Rubén Tornero, Quality Director.

During the course of the inspection, the following personnel among other provided us with relevant information related to the firm's background or in their area of expertise:

Mrs. Claudia Alcalá - Stability Head. Ms. Alcalá provided information regarding stability studies. Ms. Alcalá reports to Mrs. Rocío Saucedo, Analytical Control Manager.

Mrs. Ábida Carrillo - Quality Control Manager. Mrs. Carrillo provided information regarding the laboratory activities as well as specifications and analytical methodologies. Mrs. Carrillo reports to Rubén Tornero, Quality Director.

Mr. Elías Fragoso - Analytical Development Head. Mr. Fragoso provided information regarding the validation of analytical methods. Mr. Fragoso reports to Mrs. Rocío Saucedo Rojas, Analytical Control Manager.

Mrs. Diana Hermosillo - Documentation Supervisor. Mrs. Hermosillo provided information pertaining to release of finished product procedures. Mrs. Hermosillo reports to Mr. Rafael Castañeda, Quality Assurance Manager.

Mr. Gabriel Garate - Computerized System Validation Head. Mr. Garate provided information regarding the validation of the Empower 3 system used in the firm's HPLC equipment. Mr. Garate reports to Mr. Luis Alfredo Hernández, Validation Manager.

Mr. Miguel Madrigal - Engineering and Maintenance Manager. Mr. Madrigal provided information regarding the firm's HVAC system for Line 1. In addition, Mr. Madrigal also provided information regarding the firm's water system. Mr. Madrigal reports to Mr. Carlos Martínez, Operations Director.

Mr. Omar Mayoral - Production Manager. Mr. Mayoral provided information relative to the firm's manufacturing areas and production procedures. Mr. Mayoral reports to Mr. Carlos Martínez, Operations Director.

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Mrs. Gabriela Morales – Annual Product Report Specialist. Mrs. Morales provided information related to the firm's annual product reports procedures and documentation. Mrs. Morales reports to Mrs. Diana Hermosillo, Documentation Supervisor.

Mrs. Sofía Muñoz – Critical Systems Validation Chief. Mrs. Muñoz provided information relative to the firm's HVAC system performance validation. Mrs. Muñoz reports to Mr. Luis Hernández, Validation Manager.

Mrs. Adriana Prieto – Quality Assurance Coordinator. Mrs. Prieto provided information relative to the firm's deviation investigation procedures. Mrs. Prieto reports to Mr. Rafael Castañeda, Quality Assurance Manager.

Mrs. Rocío Saucedo Rojas - Analytical Control Manager. Mrs. Saucedo provided information regarding methods validation and stability programs. Mrs. Saucedo reports to Rubén Tornero, Quality Director.

Mr. Eduardo Vera - Warehouse Supervisor. Mr. Vera provided information regarding materials receiving and storage as well as usage history of materials. Mr. Vera reports to Mrs. Alma Delia Yañez, Warehouse Chief.

## **BUILDINGS AND FACILITIES**

Laboratorios Sophia S.A. de C.V. manufacturing facilities are located within an industrial area located at the outskirts of Zapopan, State of Jalisco. The whole industrial manufacturing complex consists of one lot with a total built area covering approximately 30,000 m<sup>2</sup> (see Exhibit 4). Physical facilities including manufacturing operations for finished products, warehouses, laboratories, and administrative offices are housed in facilities covering 20,000 m<sup>2</sup>.

The firm's finished ophthalmic products production and packaging operation area for products covered during this EI are located within the firm's facilities designated as *Edificio Manufactura de Oftálmicos* measuring 3,844 m<sup>2</sup> (see Exhibit 4). This area consist of multi-room building dedicated to the production of sterile ophthalmic solutions, including weighing of raw materials, compounding of bulk solution, filling, and primary and secondary packaging of finished products.

The firm's entire facilities include parking areas, administrative offices, a cafeteria, the quality control laboratory, and production areas. The firm has also meeting rooms, administrative offices, training rooms, storage areas for raw materials packaging components

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and finished products.

## **MANUFACTURING/DESIGN OPERATIONS (RNN)**

Laboratorios Sophia S.A. de C.V. is engaged in the manufacture of sterile OTC ophthalmic solutions for the domestic and international markets. The firm is also engaged in the manufacture of corticosteroid products for the domestic market only. We focused the inspection on the production operations of Manzanilla Sophia 0.1% and Nazil Ofteno 0.02%.

Manzanilla Sophia is a sterile ophthalmic drug product labeled as a homeopathic drug with a potency of 3X (1/1000) chamomile (*Matricaria chamomilla*) diluted in water for injection (0.095 g/100 ml). This product is indicated to refresh and replenish moisture to eyes. This OTC product contains chamomile tincture as its active ingredient.

Nazil Ofteno 0.02% is a sterile ophthalmic drug product which when applied topically to the mucous membranes of the eye, causes transient constriction of conjunctival blood vessels. This OTC drug product contains naphazoline hydrochloride (0.02g /100 ml) as its active ingredient according to OTC monograph 21 CFR 349.18(b) for ophthalmic vasoconstrictor products for over-the-counter use. It should be noted that the firm ceased the production of this product for exportation in the US as reported under the **HISTORY** caption of this EIR.

A GMP inspection for the above ophthalmic solutions was conducted in accordance with compliance program 7356.002A, Sterile Drug Process Inspections and covered the Quality, the Production, the Materials, the Facilities and Equipment, and the Laboratory Controls systems and covered profile SLQ.

## **QUALITY SYSTEM (RNN)**

Laboratorios Sophia S.A. de C.V. Quality Assurance unit is responsible for the firm's quality assurance operations. This unit is headed by Mr. Rafael Castañeda, Quality Assurance Manager (see Exhibit 5). Mr. Santillán reports to Mr. Rubén Tornero, Quality Director. The whole unit including QA, Documentation, Quality Systems, Continuous Improvement, and Raw Materials and Contractors has approximately 21 employees reporting to Mr. Castañeda.

The firm's Quality Assurance Unit has the responsibility and authority to review and approve all procedures and specifications impacting the manufacture of finished drug products produced at the plant. Coverage of the firm's Quality System included annual product review, recall procedure, batch production record review, deviations and change control procedures.

***Annual Product Review***

Laboratorios Sophia S.A. de C.V. has a written procedure describing the criteria used to prepare and document Annual Product Review reports (APR's). These reports are prepared under the responsibility of the Quality Assurance Unit in accordance with procedure Code PNO-SD-0428 version 7, effective 03/31/2015, "Revisión Anual de Producto". During the course of this EI, the following Annual Product Reviews were reviewed:

| Product Name           | Date Prepared | Period Covered                 |
|------------------------|---------------|--------------------------------|
| Manzanilla Sophia 0.1% | 05/24/2013    | April 1, 2012 – March 31, 2013 |
| Manzanilla Sophia 0.1% | 08/10/2015    | April 1, 2013 – March 31, 2015 |
| Nazil Ofteno 0.02%     | 05/28/2013    | April 1 2012 – March 31, 2013  |
| Nazil Ofteno 0.02%     | 08/10/2015    | April 1, 2014 – March 31, 2015 |

The above APR reports contained information relative to the product's manufacturing operations. The reports contained the following data: product description and packaging configuration, expiration date, amount of batches produced; manufacturing flow chart, status of process validation, status of method validation, change controls, bulk yield, analytical results of finished products, deviations, OOS, CAPA's, stability, returns, complaints, recalls and pharmacovigilance reports. The following areas were further subject of review: deviations, change controls implemented, release of finished products and review of batch production records. These areas will be discussed under the change control, batch production and control records review and batch production records under the **Quality** and the **Production System** captions of this EIR.

Review of the above APR's revealed the amount of lots manufactured during the specified period. For example:

| Product Name           | Period Covered                 | Amount of Lots Manufactured |
|------------------------|--------------------------------|-----------------------------|
| Manzanilla Sophia 0.1% | April 1, 2012 – March 31, 2013 | 5                           |
| Manzanilla Sophia 0.1% | April 1, 2013 – March 31, 2015 | 1                           |
| Nazil Ofteno 0.02%     | April 1 2012 – March 31, 2013  | 3                           |
| Nazil Ofteno 0.02%     | April 1, 2014 – March 31,      | 0                           |

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|  | 2015 |  |
|--|------|--|

Concerning Nazil Ofteno 0.02%, the firm's management explained that since 2014 this OTC product has not been manufactured by the firm. They also confirmed that the firm does not contemplate to manufacture this product for the US market. Attached as Exhibit 1 is a copy of CDER Direct Electronic Submission Portal showing that market end date was 04/29/2015.

Further review of the above Annual Product Reports revealed that in general, they are consistent with FDA expectations. The review also disclosed that information documented on the APR's corresponded with the information documented in actual production records kept for each dosage form lots.

#### ***Recall Procedure***

Laboratorios Sophia S.A. de C.V. has a written procedure defining the circumstances under which a recall of finished OTC products should be considered. The firm's "Retiro de Producto", code PNO-SD-0596 version 2, effective September 29, 2014 establishes that the Quality Assurance unit and the Regulatory Liaison are responsible to evaluate the information, how the recall should be initiated, and who should be informed about the recall. The SOP also establishes that recalled products will be destroyed after Quality Assurance assures that recall is concluded. The procedure further defines the types of recalls in three classes ranging from the highest probability in causing adverse events to the less impact: class1, class 2 and class 3.

The procedure also provides to conduct a mock recall check exercise once a year for pharmaceutical products. According to the SOP, the firm's Quality Assurance Manager and the Regulatory Liaison are responsible to coordinate all activities relative to conduct the mock recall. I selected to review records documenting a recall exercise made in 2014 for Deltomick Ungena 3 expiring 02/26/2016 g distributed in Spain. The review disclosed that the exercise was conducted in accordance with the SOP and records showed the steps followed by the firm's Quality Assurance and the Regulatory Liaison and the customer.

According to the reviewed Annual Product Review reports, no finished lots had been recalled in 2013 - 2014. In addition, no recalls had been initiated in 2015 as indicated by the firm's management. Further review of production and in-process, and laboratory control records for sterile OTC products covered during this inspection demonstrated that these pharmaceutical products have been found within specifications and, consequently, no recalls had been initiated by the firm.

Further review of the firm's recall procedure revealed that this SOP fails to include a provision or guidelines instructing how to handle a recall of products exported to the US. This deficiency was brought to the attention of the firm's management as a verbal observation. Mr.

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Rafael Castañeda, firm's Quality Assurance Manager, stated that although the recall SOP contemplates products exported, admitted that it does not specify products exported to the US. He affirmed that they will revise the SOP to include instructions to conduct a recall of ophthalmic OTC products exported to the US.

***Batch Production and Control Records Review***

Laboratorios Sophia S.A. de C.V. has a written procedure in place entitled "Dictamen de Producto", code PNO-SD-0676 effective October 31, 2012 dedicated to establish proceedings for the review and release of finished product lots manufactured at the site prior to distribution. The procedure requires that in order to release a finished lot, the following records must be reviewed as part of the release process: raw material labels, batch production, product's physicochemical and microbiological laboratory records, environmental monitoring and packaging records. The SOP also specifies that OOS, deviations and change controls submitted during the manufacturing process must have been documented, investigated and closed prior to the release of a finished product.

Review of the manufacturing operations along with analytical data developed by the Quality Control laboratory is done by QA prior to its release for final review and printing of the batch's CoA. Production records for finished products are reviewed by the QA unit along with all packaging and quality control records to determine the lot's status. The review of these records is documented in the firm's form "Documentación Expediente de Proceso Productos USA", form FRG-SD-0765. This form indicates that among the items that must be reviewed are: quality control documents, production records, environmental monitoring, primary and secondary packaging. After the document review is completed, documents are filed in an envelope, and stamped as approved, signed by QA, and the batch status is changed in SAP. This change makes the finished product lot available for shipping and distribution.

A review of all production and packaging documents related to the following finished OTC lots manufactured in 2012 through 2014 was made:

| Finished Product       | Lot Number | Manufacturing Date | Date review of Laboratory Data was Completed | Date released |
|------------------------|------------|--------------------|----------------------------------------------|---------------|
| Manzanilla Sophia 0.1% | 4009778    | 04/02/2012         | 04/17/2012                                   | 04/20/2012    |
| Manzanilla Sophia 0.1% | 4009388    | 01/12/2012         | 01/27/2012                                   | 01/31/2012    |
| Manzanilla Sophia 0.1% | 4012063    | 12/19/2013         | 01/03/2014                                   | 01/07/2014    |
| Nazil Ofteno 0.02%     | 4009780    | 04/03/2012         | 04/18/2012                                   | 04/20/2012    |
| Nazil Ofteno 0.02%     | 4011267    | 04/29/2013         | 05/14/2013                                   | 05/14/2013    |
| Nazil Ofteno 0.02%     | 4010088    | 07/10/2012         | 07/25/2012                                   | 07/26/2012    |

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The review of the above records revealed that all production and quality control records for these finished OTC lots were reviewed and documents were verified for completeness by the Quality Assurance unit prior to their release in accordance with the established procedure.

### ***Change Control Procedures***

Change Control Procedures are handled by the firm's PNO-SD-0430 version 3 effective January 13, 2015, "Control de Cambios". The SOP establishes the guidelines needed to handle and process change controls. The procedure also establishes that changes in documents, processes, documents, manufacturing or laboratory equipment, critical systems, or any change required by regulatory requirements or corrective actions must be handled in accordance with this SOP. These changes must be reviewed by a Change Control Committee, the Regulatory Liaison and approved by the site Quality Assurance in order to guarantee the consistency and control of manufacturing operations.

Changes are classified in three different types: Minor, Moderate, and Major. Minor changes are those that may have minimal impact in the quality, identity, purity, and potency of pharmaceutical products. Moderate changes are those that have moderate potential in causing an adverse effect in the identity, purity, quality, or potency in the pharmaceutical product that may influence in the safety and efficacy of the product. Major changes are those changes that are expected to have a potential impact in the product's purity, identity, quality and potency that could affect the safety and effectiveness of pharmaceutical products.

Changes may be initiated by personnel from the firm's different divisions. Processing of proposed changes is subject to three phases: preliminary assessment, approval and implementation. Each phase should be documented from the initial submission to the end. During the preliminary assessment, the proposed change is identified with a request for change code assigned by the firm's Compliance Specialist. Once received, the proposal is reviewed by the Compliance Specialist and assigned a change code consisting of five numbers by their computer system. The first two numeric characters identify the last two numbers of the current year, while the rest three characters is a consecutive number. After a change control number is assigned, the change control request is referred to the Change Committee which will decide if the change proposal is approved. Once the proposal is approved, the change control is referred to the requestor for follow-up and implementation. As soon as the change is completed and the corrective actions are verified by the Compliance Specialist in accordance with the original proposal, all documents concerning the change are referred to the QA unit for final review and concurrence. Once approved by QA, documents are returned to the Compliance Specialist and the change control is closed.

Changes requiring more time than specified in the original proposal, or there is a delay in the activities, an extension must be requested to the Compliance Specialist using form FRG-SD-0544VV. A justification to support the extension must be documented. In the event that more time is needed, a second extension could be granted by the Compliance Specialist

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with the concurrence of the Quality Assurance Manager and a third extension could be granted with the concurrence of the firm's Regulatory Liaison.

During the course of this inspection, the following changes were reviewed: 14-009, 14-065, 14-249, 15-016 and 15-329. Review of all documents related to the above changes revealed that these were submitted, evaluated and approved by the Change Control Committee, and closed in accordance with the firm's procedure. Review of changes requiring an extension disclosed that these were reviewed by Compliance and concurrence obtained from Quality Assurance. Nevertheless, review of the above records revealed that the firm's change control procedure does not mention or specify that the status of those changes requiring an extension be documented with a proposed target or due date on the extension request. Mrs. Alicia Morfin, firm's Compliance Manager, admitted that the status of those pending change controls was not required in the procedure. She stated that the current SOP will be revised to include a statement requiring the status of the change when requesting an extension. Before the conclusion of the inspection, a copy of the draft revised procedure was shown to me (version 4) in which section 7.6.16 states that in the event a target or due date is not provided by the requester, the Compliance Specialist must make it clear in the change request.

***Deviation Investigations***

Guidelines needed to handle deviation investigations are processed in accordance with the firm's written procedures in place entitled "Sistema de Notificación", code PNO-SD-0431 version 2, effective October 7, 2014 and "Manejo de Desviaciones" code PNO-SD-0432, version 2 effective January 16, 2015. The first procedure covers all problems, anomalies, defects, or any other discrepancy observed in the production areas, for instance, compounding, filling and packaging. This procedure establishes that the impact of the event must be defined in one of three alternatives: primary quality, secondary quality or other. Primary quality is defined as any condition or circumstance that imminently has a high risk in the safety, and compliance with product's specifications or regulatory requirements. Secondary quality are those events that implies an impact in the product's packaging, while other means all additional events having an impact over processes, regulation, procedure, results or other conditions. The notification documenting the non-compliance event must be submitted to the QA unit using form FRG-SD-0591, titled Notification Report. The type of event must be determined using a table listing all events by number, classification, and quantified through the determination of three factors such as severity (insignificant, low, moderate, significant, high), assurance of detection (very high, high, low, very low, and none) and occurrence (insignificant, low, moderate, high, frequent). These three indicators must be multiplied to calculate the risk level (critical, mayor, or minor). Once the report is filed, the notification is reviewed by the QA unit along with the responsible area to determine if a deviation or an out-of-specification result report must be prepared. Each notification is assigned a 7 alphanumeric number starting with N, which means "notification"; followed by six numbers from which the first two numbers correspond to the last two digits of the year, while the rest four numbers are a consecutive numeral.

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Deviations are those situations that represent a non-conformance in a procedure, policy, GMP's, validated process specifications or environmental conditions that not always develop in an out-of-specification product. These situations are then handled in accordance with the firm's procedure titled "Manejo de Desviaciones", code PNO-SD-0432. Situations where there is an OOS product as a result of analytical or microbiological tests, must be handled in accordance with the firm's procedure for non-conforming product, code PNO-SD-0647.

Once a notification identifies that a deviation report must be prepared, then it is assigned a Deviation Report code number ("Reporte de Desviación" or RDD). This code starts with RDD, followed by two digits which identify the last two numbers of the current year, followed with a consecutive number consisting of three characters. Once the event is coded, the Quality Unit refers the deviation to the responsible individuals that will identify the root cause of the deviation. Deviations must be investigated, and if corrective actions are recommended, these must be handled in accordance with SOP "Manejo del Sistema de Acciones Correctivas y Preventivas (CAPAS)", code PNO-SD-0436, version 4, effective 09/02/2013 and discussed and approved by Quality Assurance prior to their implementation. Deviation reports must be prepared in 30 calendar days and submitted to the QA unit for review and final filing.

During the course of the inspection, the following non-conformance events were reviewed:

| Deviation Number | Event                                                            | Date Reported |
|------------------|------------------------------------------------------------------|---------------|
| RDD-14-087       | Environmental Monitoring not realized in accordance with the SOP | 06/02/2014    |
| RDD-14-178       | Yield out-of-specification                                       | 10/27/2014    |
| RDD-15-003       | Release of finished product without placing it in quarantine     | 12/16/2014    |
| PNC-14-063       | Weights in the lower limit                                       | 04/25/2014    |
| PNC-14-088       | Finished Product with Leaks                                      | 05/30/2014    |
| PNC-15-093       | Product failed the description test                              | 07/26/2015    |

In addition, the following CAPA's were reviewed during the course of this inspection:

| CAPA Number | Event                                                      | Date Reported |
|-------------|------------------------------------------------------------|---------------|
| AC-14-003   | Specifications Revision in Master Batch Production Records | 02/13/2014    |
| AC-14-012   | Revision of Synalum Manufacturing                          | 08/12/2014    |

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|           |                                   |            |
|-----------|-----------------------------------|------------|
|           | process                           |            |
| AC-15-002 | Transfer of 5 packaging materials | 04/09/2015 |

Review of the above deviation reports and CAPA's revealed that these were previously reported as notifications and reported, reviewed, approved as deviations and corrective actions implemented in accordance with the firm's procedure. In addition, trainings delivered were properly documented. No discrepancies were observed.

**Facilities and Equipment System (RNN)**

Laboratorios Sophia S.A de C.V. Engineering Unit is responsible for the firm's maintenance of facilities and equipment. This unit is headed by Mr. Miguel A. Madrigal, Engineering and Maintenance Manager. Mr. Madrigal reports to Mr. Carlos Martínez, Operations Director (see Exhibit 6). This unit has 29 employees reporting to Mr. Madrigal.

***Inspection of Facilities***

We inspected the firm's manufacturing facilities on the first day and subsequently during the course of the inspection. Manufacturing operations for ophthalmic products are performed in specifically designated area located at the firm's second level (see Exhibit 7, areas designated as "Edificio de Producción de Oftálmicos"). Facilities appeared to be well maintained and equipped with adequate lighting, air handling systems, WFI, steam, and manufacturing utensils. Equipment installed appeared to be of adequate design, size and location for the production of finished sterile ophthalmic solutions.

***HVAC System***

The firm has a system in place to supply filtered air to critical areas through HEPA filters under constant positive pressure (see Exhibit 8). The firm's compounding and filling area for ophthalmic products exported to the US are located at Line 1, where the filling operations are made has been designated as Class 100 (see Exhibit 9). According to Mr. Madrigal, Line 1 HEPA filter system was installed in 2007 and consists of 10 H-14, HEPA filters installed with 99.97% efficiency. He also affirmed that these filters had rectifiers installed which provides a consistent, uniform laminar flow. He also added that the system is also calibrated to maintain the pressure in a consistent manner.

The firm utilizes external air as its source of air for Class 100 processing areas. Air is pre-treated through two UMA units (UMA-OFT-13 and UMA-OFT-14) which provide the first filtering stage with an efficiency of 35% (see Exhibit 10, pp. 4 – 5). External air is collected and filtered, heated and dehumidified at a temperature of 8°C and pumped at a pressure set point of 160 pascals with a capacity of 53,000 m<sup>3</sup>/h.

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Once filtered, air is transferred to the manufacturing area. During manufacturing operations, 80% of the air is recirculated, while the remaining 20% is new filtered air. Recirculated air is cooled, warmed and filtered utilizing an UMA-OFT-01 unit (see Exhibit 10, p. 6). This unit is responsible to provide two pretreatment stages; the first stage has an efficiency of 85%, while the second stage has an efficiency of 98% with a capacity of 31,739 m<sup>3</sup>/h.

Maintenance of HVAC ophthalmic systems is monitored through the firm's Preventive Annual Maintenance program. This program is monitored via a module in SAP computer system that manages maintenance of facilities. UMA units, HEPA filters as well as other critical equipment are included in this maintenance program. According to this program, UMA units are calibrated every 6 months, while the HEPA filters are calibrated once a year. I requested to see maintenance records for UMA-OFT-01, and laminar flow maintenance records for HEPA filters located under the compounding and the filling line (FLU-LA-01A and FLU-LA-01B) for the years 2012 – 2014. The review revealed that maintenance was performed in accordance with the procedure. Systems were verified and parts were replaced when necessary and documented as part of the maintenance program.

I also reviewed the firm's qualification of the air conditioned and HVAC system. This qualification is performed on an annual basis in accordance with procedure "Validación del Sistema de Aire Acondicionado y Ventilación HVAC", code PNO-SD-0409, version 8, effective March 25, 2015. This procedure provides for the annual performance qualification of the HVAC system installed in critical areas, such as Lines 1 – 5 dedicated to the manufacture of sterile ophthalmic products. According to the SOP, the system is evaluated once a year for the following parameters, among others: air flow speed, air volume, temperature and relative humidity of air, non-viable and viable particles, differential pressure, laminar air flow and integrity of HEPA filters. The procedure specifies the method to perform these tests and the acceptance criteria for each test. Integrity of HEPA filters in Class 100 areas is performed every 6 months. Anomalies observed during the qualification exercise must be handled as a deviation in accordance with the firm's deviation procedure. I reviewed the last reports during the years 2014 and 2015 for Line 1. The review revealed that all tests were performed and documented in accordance with the SOP. Non-conformances were handled as deviations and documented in accordance with the firm's procedures.

***Water for Injection System (WFI)***

Water for Injection (WFI) is utilized during the manufacturing process of ophthalmic sterile solutions. The firm analyzes WFI in accordance with the parameters described in the Mexican and USP pharmacopeias.

The firm's WFI water system was inspected during the course of the inspection. The WFI system is located the firm's first level area. According to Mr. Miguel Madrigal,

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Engineering and Maintenance Manager, the firm obtains approximately 430 m<sup>3</sup> per day of water obtained from one well as the primary source. Well water is stored in one of three cisterns after chlorine is added as a pretreatment (see Exhibit 11, identified as "Cisterna 1, 2 and 3"). Pretreated water is filtered and subsequently passed through reverse osmosis system to obtain purified water which is stored in a 3,500 liters capacity stainless steel tank. Purified water may be diverted to generate pure vapor, while purified water intended to be utilized in the manufacture of WFI is further distilled through a multiple distillators unit (see Exhibit 11, "Destilador de Múltiple Efecto"). Distilled water that will be used by the ophthalmic manufacturing area is stored in a stainless steel holding tank with a capacity of 4,000 liters identified as "Tanque de Almacenamiento AFI Oftálmicos" and distributed to the different points of use (see Exhibit 11, "Loop Distribución Oftálmicos"). This holding tank has a 0.22 micrometer vent filter whose temperature is continuously monitored. Water is recirculated at 80°C to the points of use and recirculated back into the holding tank.

The WFI system has instruments installed that monitor water quality for pH, conductivity, flow, temperature and TOC on a continuous basis. Water level in the storage tank is also monitored during the process. Values for these parameters are recorded on a periodic basis as part of the WFI process controls.

Maintenance of the firm's WFI system is monitored through the firm's Preventive Maintenance Program. This program is monitored via a module in SAP computer system that manages maintenance of facilities. Distillators, vapor generators, multimedia filters, reverse osmosis, and purified water system are included in this maintenance program. According to this program, maintenance must be made to distillators, and reverse osmosis every 3 months. I requested to see maintenance records for the distillers and for the reverse osmosis for the year 2015. The review revealed that maintenance was performed in accordance with the procedure. Systems were verified and parts were replaced when necessary and documented as part of the maintenance program.

**Production System (RNN)**

Production of sterile ophthalmic solutions is made under the firm's Manufacturing unit whose operations are the responsibility of Mr. Omar Mayoral, Production Manager. Mr. Mayoral reports to Mr. Carlos Martínez, Operations Director (see Exhibit 12). This unit has seven supervisors and 104 employees reporting to Mr. Mayoral.

***Inspection of Manufacturing Operations***

The firm's ophthalmic manufacturing areas were inspected during the initial walk-through of the firm's manufacturing activities. Various production activities were observed throughout the walk-through, including gowning of employees, compounding and filling of ophthalmic solutions, and labeling, primary and secondary packaging of sterile solutions.

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Production equipment was identified and instruments used in various steps of the manufacturing process were identified and showed tags documenting the calibration date. Employees were observed following gowning procedures to access the firm's filling and inspection areas. No objectionable conditions were observed during the walk-through of the production areas.

***Manufacturing Process for Ophthalmic Solutions***

Manufacture of sterile ophthalmic solutions for exportation to the US is performed in Line 1 located on the second level (see Exhibit 7, "Edificio de Producción de Oftálmicos"). Mr. Omar Mayoral, firm's Production Manager and Mr. Cristóbal Díaz, Production Supervisor, explained the product's production operations during the initial walk-through of the firm's manufacturing plant. According to Mr. Díaz, manufacturing process for ophthalmic solutions consists of three stages: compounding of solution, filling of solution in vials, and labeling, primary and secondary packaging (see Exhibit 13).

The compounding stage initiates when raw materials are weighed at the firm's Warehouse and further transported to the Production Area. During the manufacture of Manzanilla Sophia 0.1%, raw materials are added in a Class 1000 area. In this space, raw materials such as chamomille, monohydrate sodium monobasic phosphate, anhydride sodium dibasic phosphate, sodium chloride, and benzalkonium chloride 50% solution, are added and mixed with WFI contained in stainless steel tank during the compounding stage. The remaining portion of WFI is added and the solution is maintained between 20 – 35°C at 105 – 115 revolutions per minute (rpm). The solution is agitated for additional 60 minutes at 75 – 85 rpm's and at the end of this process; an in-process sample is collected for microbiological analysis by Quality Assurance. If product is found to comply with specifications, bulk solution is released and moved to a stainless steel holding tank which is transferred to the filling area. Theoretical batch size is 500 liters.

The filling operation initiates when sterile hoses are connected to the holding tank containing the solution. The filling equipment is surrounded with a clear plastic curtain which keeps the filling operations under a Class 100 area. Outside the curtain, the area is classified as a Class 1,000. During the filling operation, bulk solution is aseptically filtered through a 0.22 µ filter prior to filling, and the solution is circulated to the filling machine where containers are automatically filled through the filling terminal via 4 syringes. Subsequently, a cap is placed in the opened container and sealed. During the filling operations, samples of sealed containers are collected for volume, sterility, torque, hermeticity, and chemical testing. Theoretical batch size is 32,145 units.

Filled containers are transferred to the next contiguous area where they will be labeled, and individually packaged, and subsequently subject to secondary packaging. During the primary packaging step, lot number and expiration date and container weight is

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manufacturing instructions, critical point parameters, established time limits for completion of the different phases of production, and spaces where employees must record and sign to certify the performance of the manufacturing steps. The records also provide spaces for the signature of the second employee verifying the performance of the different stages of production.

#### ***BATCH PRODUCTION RECORDS***

Batch production records for Manzanilla Sophia 0.1% and Nazil Ofteno 0.02% were reviewed for each manufacturing step from the initial compounding to the finished sterile product. For instance, review of abiraterone acetate batch production records revealed the following data:

| <b>Product</b>         | <b>Bulk Solution Lot Number</b> | <b>Date Compounded</b> | <b>Finished Product Lot number</b> | <b>Date Filled</b> | <b>Date Packaged</b> |
|------------------------|---------------------------------|------------------------|------------------------------------|--------------------|----------------------|
| Manzanilla Sophia 0.1% | 7007883                         | 11/06/2012             | 4012063                            | 11/07/2012         | 11/07/2012           |
| Manzanilla Sophia 0.1% | 7008267                         | 05/02/2013             | 4011271                            | 05/03/2013         | 05/03/2013           |
| Manzanilla Sophia 0.1% | 7007883                         | 11/06/2012             | 4010683                            | 11/07/2012         | 11/07/2012           |
| Nazil Ofteno 0.02%     | 7008264                         | 04/29/2013             | 4011267                            | 04/30/2013         | 04/30/2013           |
| Nazil Ofteno 0.02%     | 7007510                         | 07/10/2012             | 4010088                            | 07/11/2012         | 07/11/2012           |
| Nazil Ofteno 0.02%     | 7007328                         | 04/03/2012             | 4009780                            | 04/04/2012         | 04/04/2012           |

Review of all pertinent production records throughout the manufacturing process for all lots disclosed that these operations were performed according to the manufacturing instructions. In-process controls are established and documented. Critical steps were signed by the operator and confirmed by a second employee. In-process samples were also collected and analyzed in accordance with the established procedures. Manufacturing equipment was properly identified during all the manufacturing steps.

#### **Materials System (APZ)**

Laboratorios Sophia S.A. de C.V. Warehouse Unit is responsible for the firm's receipt, handling and storage of raw materials and packaging components as well as for the storage

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monitored. Individual packaging as well as secondary packaging is a manual operation. Once secondary packaging operations are concluded, product is transferred to the finished product warehouse awaiting release for further distribution.

Operational parameters such as raw materials amount, temperature, rpm's, and time are automatically controlled by recipes contained in the HMI SCADA computer system. Filter integrity is tested before and after filling operation by QA personnel according to the firm's procedure "Control de Producto en Proceso de Formulación y Envasado" code PNO-SD-0577, version 4, effective June 1, 2015.

Cleaning of manufacturing equipment is automatically performed via cleaning in place procedures. After the cleaning cycle is completed, samples are collected for conductivity. Utensils are cleaned in a designated area using WFI at approximately 80°C. Once cleaned, utensils are placed in a clear plastic bag, sealed and labeled as cleaned, assigned an expiration date of 7 days and further stored in a separate room dedicated for the temporary storage of cleaned materials ("Area Temporal para Material Limpio").

**Master Production Records**

Master Production Records (MPR's) are handled by the firm's written procedures "Control de Documentos", code PNO-SD-0421, version 4, and effective March 2, 2015. This SOP establishes the guidelines describing the control, revisions and printing of Master Production Instructions. The SOP's also define that any revision made to Master Production Instructions must be handled in accordance with the firm's Change Control procedure.

Master Production Records consist of the following: Material for Bulk Production Material for Filling, Bulk Compounding Manufacturing Instructions, Filling Manufacturing Instruction, and Finished Product Packaging Order. The firm has in place the following Master Production Records utilized for the manufacture of Manzanilla Sophia 0.1%:

| Document                         | Effective Date | Product Code |
|----------------------------------|----------------|--------------|
| Orden de Proceso                 | 12/19/2013     | 1027647      |
| Orden de Proceso                 | 12/19/2013     | 1027648      |
| Instrucción de Producción        | 04/07/2015     | 70263-000-02 |
| Instrucción de Envasado          | 08/26/2015     | 40848        |
| Instrucción de Acondicionamiento | 08/03/2015     | 40848-000-03 |

The above MPR's were subject of my review. The review revealed that they have been prepared by the firm's Production, and approved by the Regulatory Liaison and the QA unit in accordance with the SOP. The review also revealed that the records contain

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and shipping of finished products. The firm's warehouse facilities are divided in two storage areas: raw materials and finished products. This unit is headed by Mr. Juan G. Hernández, Planning Manager. Mr. Hernández reports to Mr. Carlos Martínez, Operations Director (see Exhibit 14). This unit has 34 individuals reporting to Mr. Hernández.

***Receipt of Raw Materials***

According to Mr. Eduardo Vera, Warehouse Supervisor, the materials are received in the warehouse through three gates dedicated to the receipt of raw materials. Once the materials arrive, the warehouse personnel reviews the documentation and performs a visual inspection, and after confirming this information, a label is generated indicating the following: material description, code, supplier lot number, number of containers, storing conditions and expiration date. This label is attached to all the containers and the material is entered in SAP system with a Quarantine status. The Quality Assurance unit further inspects the materials and collects a sample. After the appropriate testing is performed, Quality Assurance unit is responsible for changing the material status in the SAP system.

The warehouse also has a cold room and a freezer for raw materials that require being stored under those conditions. There is also a sampling chamber and a clean room for sterile raw materials.

Finished product is stored in a different warehouse supervised by Ms. Alma Yáñez, Finished Warehouse Chief. This warehouse is connected to the manufacturing site. Finished product is visually inspected by the warehouse personnel and the documentation is reviewed, and if the information corresponds, then the data is entered into SAP with a Quarantine status until QA releases the product. Non-conforming product is kept in "caged" locations; at the time of this inspection the cages were empty.

Temperature and relative humidity is monitored in both warehouses using data loggers. Data is downloaded on a daily basis and reviewed for maximum and minimum values, which are recorded in a logbook named "Record of environmental conditions monitoring in the warehouse", along with the data logger ID number and calibration dates.

***Storage of packaging materials under quarantine until tested or examined***

During the course of the inspection, I reviewed the receiving documents, the certificates of sterilization when applicable, history in SAP directly in the system, the first CoA's used to release the materials for use prior to be utilized in production and the corresponding supportive analytical data for packaging materials of Manzanilla Sophia 0.1% and Nazil Ofeno 0.02%. In the following table, there is a summary of the materials reviewed and the dates found in the different documents. These materials were used in the

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manufacture of Manzanilla Sophia 0.1% lot 4013510 and Nazil Ofteno 0.02% lot number 4011267.

| Material                           | Lot number | Receiving date | Date Released by QA |
|------------------------------------|------------|----------------|---------------------|
| Bottle 15 ml irradiated Nazil      | 3014818    | 01/15/13       | 01/18/13            |
| Insert irradiated Nazil            | 3014983    | 02/01/13       | 02/03/13            |
| White cap irradiated Nazil         | 3015143    | 03/04/13       | 03/06/13            |
| Bottle 15 ml irradiated Manzanilla | 3018582    | 11/13/14       | 11/19/14            |
| Insert irradiated Manzanilla       | 3018555    | 11/05/14       | 11/10/14            |
| White cap irradiated Manzanilla    | 3018634    | 11/25/14       | 11/28/14            |
| Label Nazil Ofteno USA             | 3013123    | 05/04/12       | 05/17/12            |
| Warranty Band Sophia               | 3015120    | 03/01/13       | 03/05/13            |
| Instructions Nazil                 | 3012673    | 02/28/12       | 02/28/12            |
| Box Nazil Ofteno USA               | 3013185    | 05/17/12       | 05/21/12            |
| Multiple box Nazil Ofteno USA      | 3008427    | 05/11/10       | 05/11/10            |
| Label Manzanilla Sophia USA        | 3016659    | 11/28/13       | 12/04/13            |
| Warranty Band Sophia               | 3015120    | 12/02/14       | 12/05/14            |
| Instructions Manzanilla            | 3016732    | 12/11/13       | 12/12/13            |
| Box Manzanilla Sophia USA          | 3016710    | 12/05/13       | 12/09/13            |
| Multiple box Manzanilla Sophia USA | 3019169    | 03/12/15       | 03/17/15            |

The review of these documents disclosed that the items were inspected and the review of receiving documents and the dimensional tests were approved by QA. The review also revealed that they were received and inspected according to the firm's procedure. However, the CoA's of the primary packaging components were approved by QA before all the corresponding tests were finalized. This will be further discussed under the **OBJECTIONABLE CONDITIONS** caption of this EIR.

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### ***Microbiological Control of Purified Water System***

I reviewed the microbiological control of the firm's purified water system used in the manufacture of Water for Injection (WFI). According to Mrs. Ábida Carrillo, Quality Control Manager, the water is tested daily in the sample points indicated in the procedure titled "Water sampling in the treatment plant, distribution network and pure steam condensates", code PNO-SD-0451 effective 08/24/2015 (Exhibit APZ 4). Water samples are collected for physicochemical and microbiology testing. I reviewed the test results and analytical data for water during the period 02/03/15 to 08/24/15. All samples appeared to be collected and tested according to the firm's procedures. No observations were made.

### **Laboratory Control System (APZ)**

The firm's Quality Control unit is responsible for analyzing and testing raw materials, in-process samples, and release testing of finished products, as well as stability samples. This unit is headed by Mrs. Ábida Carrillo, Quality Control Manager. She reports to Mr. Rubén Tornero, Quality Director (see Exhibit 15). This unit has 30 individuals reporting to Mrs. Carrillo.

### ***Inspection of Laboratory Facilities***

Mrs. Carrillo accompanied us during the inspection of the firm's laboratory facilities during the walkthrough and provided information regarding the firm's laboratory facilities and equipment. She explained the firm's laboratory organization and main processes. According to Mrs. Carrillo, samples are divided in raw materials, bulk, finished product, and packaging materials. Samples received are recorded in a specific logbook and then assigned to the analysts. Samples of bulk product are immediately assigned and tested given the need for the results to release the product for packaging, the rest of the samples are kept in a locker until the assigned analyst is ready to test them.

The firm's laboratory facilities are divided in physicochemical analysis and microbiology. During the inspection, I observed that the laboratory appears to be organized, with trained staff and equipped according to the analyses the firm indicates they perform. The equipment had calibration tags or labels indicating the calibration date and the due date for the next calibration, and all tags/labels reviewed were within calibration.

During the inspection of the laboratory, I observed a discrepancy in the lot number in the label of the buffer bottle used to calibrate the pH meter and the one recorded in the logbook. Mrs. Carrillo investigated this discrepancy and presented the results as well as evidence of changes implemented in the corresponding procedure to prevent the occurrence of this kind of discrepancies. This discrepancy was brought to the attention of the firm's management as a verbal observation.

### **Analytical data**

I reviewed the Certificates of Analysis along with specifications and raw data, consisting of original print outs of chromatograms and data retrieved from the analytical computer system. I also reviewed UV spectra, microorganism strains certificates, growth promotion reports, environmental monitoring, the logbooks of use of equipment as well as the analytical notebooks relevant to the testing of Manzanilla Sophia 0.1% and Nazil Ofteno 0.02%, finished and bulk product, for the lots specified in the following table:

| Material               | Lot                | Type of material | Specification |
|------------------------|--------------------|------------------|---------------|
| Nazil Ofteno 0.02%     | 7007510<br>7008264 | Bulk product     | 40847-000-02  |
| Nazil Ofteno 0.02%     | 4010088<br>4011267 | Finished product | 40847-000-02  |
| Manzanilla Sophia 0.1% | 7009831<br>7008267 | Bulk product     | 40848-000-00  |
| Manzanilla Sophia 0.1% | 4013510<br>4011271 | Finished product | 40848-000-00  |

The review of the data disclosed missing/repeated data in the use of equipment logbooks. These deviations were discussed with Mrs. Carrillo. She acknowledged the discrepancies and indicated that in fact, the documentation practices have been improved since the date where the discrepancies were found (2012). I verified this statement through the review of more recent records (2013 - 2015). No other observations were made.

### **Analytical Methodology**

Mr. Elías Fragoso, Analytical Development Head explained the SOP "Analytical Methods Validation" PNO-DD-0105 rev. 2 effective 10/12/2011, and presented the validation data for the methods used in Nafazoline HCl assay by HPLC and Manzanilla identification by UV spectrometry. For the latter, the validation only included the specificity parameter and a stability study of the reference solution for up to 36 hours. Nevertheless, in the practice the reference solution is used for up to six months. I discussed this practice with Mrs. Rocío Saucedo, Analytical Control Manager. She indicated that the test is based on the comparison of the wavelength of the maximum and minimum absorbance in the spectrum of the reference solution and the one of the sample, and that the correlation is always the same. However, given that there is no information supporting the stability of the reference solution, they will modify the current method in order to reflect that the solution be prepared fresh for each test. The change control and supportive draft documents were also presented by Mrs. Saucedo for my review during the course of the inspection.

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I reviewed the validation of the Empower 3 system used in the HPLC equipment in the firm. Mr. Gabriel Garate, Computerized System Validation Head, presented the validation data and supporting evidence. No observations were made.

### ***Stability***

Mrs. Rocío Saucedo, Analytical Control Manager, is responsible for the firm's stability program, as well as method validation and pilot lots development. She reports to Mr. Rubén Tornero, firm's Quality Director. Mrs. Saucedo has 38 employees reporting to her (see Exhibit 16).

The firm has a laboratory specific for this activities, and a room dedicated to the stability chambers and climatic rooms. Both the laboratory and the stability chambers room appeared to be well equipped and organized. No observations were made.

Mrs. Claudia Alcalá, Stability Head is the responsible for the stability program. She presented the information regarding the following stability studies: PRO-113-003-001-00 approved on 03/07/2011 for accelerated and long term stability of Manzanilla Sophia 0.1% and, PRO-112-002-001-00 approved on 03/02/2011 for accelerated and long term stability for Nazil Ofteno 0.02% along with their corresponding reports approved on 03/2014. Both summaries and raw analytical data were reviewed. The review of these data disclosed that tests were actually made at the corresponding time period and results were documented and reported according to the firm's SOP "Accelerated and long term stability studies" PNO 084-08-000-00.

A closer review of these records led to a verbal observation regarding the test result of nafazoline assay for the 3 months sample of the accelerated stability study. According to the records reviewed, the test dated 06/03/2011 reported an assay of 95.0% (specification 90 - 115%). A second test conducted on 06/13/2011 reported a result of 96.8%. This latter value was the result reported on the data summary, without any justification regarding the dismissal of the first result. Ms. Raquel Treviño, Stability Analyst, explained that according to the firm's internal policy, when the data obtained is different from the one of the previous station by 3% it is considered out of tendency and another analysis has to be made and the original result is changed. I explained Ms. Treviño and Mrs. Saucedo that this is not a good laboratory practice and in order to do so, an investigation supported by data and performed in accordance with an approved procedure, must be conducted.

I requested to see stability data developed for Manzanilla Sophia and Nazil Ofteno for the years 2012, 2013, 2014 and 2015. Mrs. Saucedo presented the data for the lots placed on stability on 2012, and indicated that those were all lots placed on stability. This will be further discussed under the **OBJECTIONABLE CONDITIONS** caption of this EIR.

### ***Reserve samples***

The firm has separate rooms to keep reserve samples for raw materials and those for finished products. These are monitored for temperature and relative humidity. The samples are arranged in alphabetic order organized by lot number; both rooms appeared to be well organized and clean. I requested to see reserve samples corresponding to lots 4013510 and 4011271 for Manzanilla 0.1% and 4010088 and 4011267 for Nazil Ofteno 0.02%. The four samples were presented and appeared to be in good condition. The routine inspection of the reserve samples is actually made but it is not included in the procedure. During the course of the EI, the corresponding change control and draft procedure requiring the inspection of reserve samples was presented by Mrs. Carrillo for my review.

### ***Out of Specification Results***

I reviewed the SOPs "Handling of Out of Specification Results and Out of Tendency Results" PNO-SD-0701 and "Handling of Out of Specification Results in Microbiology Area" PNO-SD-0980. I requested a list of the out-of-specification results reported during the past two years and selected five events to review the investigation reports. These reports are detailed below:

| <b>OOS number</b> | <b>Description</b>                                                               | <b>Date opened</b> | <b>Date closed</b> | <b>Root cause</b>                                                                          |
|-------------------|----------------------------------------------------------------------------------|--------------------|--------------------|--------------------------------------------------------------------------------------------|
| 15-066            | Googles swabbing on filling line 3 resulted in 25 CFU/plate (spec < 3 CFU/plate) | 03/12/15           | 03/18/15           | Microorganism found Staphylococcus epidermidis from the personnel. A deviation was opened. |
| 14-196            | Nazil Ofteno assay CV 3.7 (criteria < 2.0%)                                      | 11/19/14           | 11/19/14           | HPLC purge not properly done.                                                              |
| 14-197            | Benzalconium chloride assay, system suitability RT < 1 min (criteria > 1 min)    | 11/19/14           | 11/19/14           | HPLC purge not properly done                                                               |
| 15-082            | Nafazoline HCl assay <99% (spec. 99/110%)                                        | 03/27/15           | 03/30/15           | Wrong formula used in calculations                                                         |
| 15-044            | Oxytetracycline HCl assay 83.6% (spec. 88.2- 96.8%)                              | 02/09/15           | 02/10/15           | Balance used no appropriate for the amount weighed.                                        |

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The investigations described in the table were conducted according to the procedure; confirmed OOS results were followed by a broad investigation through the corresponding deviation. No observations were made.

## **MANUFACTURING CODES (RNN)**

The production of finished OTC products is coded through a 7 numeric character system. According to the firm's product code system, "Asignación de Número de Lote", code PNO-SD-0720 version 1, effective June 21, 2012, the first character, represent the type of material, e.g., for bulk 7, finished product, 4. The next six numbers, is a consecutive number for each product starting with 000001. For example, product lot number 4000001 designates the first order of finished product manufactured in a specific year. Lot numbers are assigned by Planning through SAP system and are printed on the finished package label.

## **REFUSALS**

There were no refusals made in connection to this establishment inspection.

## **OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE (APZ)**

There were two significant objectionable conditions observed during the course of this inspection that were reported in an FDA-483 issued to Mr. Eleuterio López Sánchez, firm's General Director during the exit interview. These deviations were quoted in bold and italic print for reference in this section. These observations were not entered in Turbo.

1. ***Your firm failed to follow written procedures intended to assess the stability characteristics of ophthalmic products. Specifically, procedure PNO 084-08-000-00 "Accelerated and long term stability studies" establishes to include one lot of each dosage and closure-container system of the products in a long term stability study every year. However, no lots of Nazil Ofteno 0.02% and Manzanilla Sophia 0.1% were included in the stability program during the year 2013. (APZ)***

I requested the stability protocols and data for the years 2012 – 2015 for Manzanilla Sophia 0.1% and Nazil Ofteno 0.02%. Mrs. Rocío Saucedo, firm's Analytical Control Manager presented protocols PRO-113-008-000-00 approved 01/06/2012 for Manzanilla Sophia 0.1% and PRO-112-006-000-00 approved 01/23/2012. I reviewed these documents along with the analytical data, and no observations were made. Mrs. Saucedo and Ms. Claudia Alcalá, Stability Chief indicated that those were the last stability protocols for the two products, given that no lots were included in the stability program for 2013 and 2015,

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Additionally, Manzanilla Sophia lot number 4013510 was manufactured on 03/24/2015 and the testing of the materials used to package this lot were finalized on 05/5015. I discussed this with Mrs. Ábida Carrillo, Quality Control Manager and Mr. Rafael Castañeda, Quality Assurance Manager, given that the packaging components were approved before the complete set of tests were conducted. Mrs. Carrillo indicated that these materials were approved for use based on the certificate of sterility from the supplier and the inspection and dimensional tests performed by QA, and that the rest of the tests were conducted to confirm the compliance of the specifications. Regarding the date on the CoA, she indicated that the SAP system requires an approved decision in order to allow the use of the materials, hence the date of approval in the CoA predated the actual analysis; however she admitted that this practice is not documented. I explained that these materials should be tested for conformity with the written specifications and that it is also acceptable using the supplier's certificates and the QA inspection, provided that it is documented and the supplier validated. Mrs. Carrillo indicated that they would develop the corresponding documentation. Exhibit APZ 2 is a copy of the CoA of the Manzanilla Sophia lot number 4013510 and Exhibit APZ 3 is the CoA and analytical report for the containers and closures used to package this lot.

## **GENERAL DISCUSSION WITH MANAGEMENT (RNN)**

On August 28, 2015 we met with Laboratorios Sophia's management to discuss the results of the on-site inspection. On behalf of the firm, the following personnel participated during the discussion:

| <u>Name</u>            | <u>Title</u>        |
|------------------------|---------------------|
| Mr. Eleuterio López    | General Director    |
| Mr. José Rubén Tornero | Quality Director    |
| Mr. Rafael Castañeda   | Quality Manager     |
| Mr. Carlos Martínez    | Operations Director |
| Mrs. Alicia Morfin     | Compliance Manager  |

As the firm's most responsible individual present at the firm, the FDA-483 was issued to Mr. Eleuterio López, General Director. Mr. López acknowledged the importance of the observations both in writing and verbal and expressed that the firm was committed to correct these deviations. He also stated that they will respond in writing in 15 days with the proposed

and no lot was placed on stability since in 2014 there were no lots manufactured of either product. I indicated Mrs. Saucedo and Ms. Alcalá that according to their SOP "Accelerated and long term stability studies" PNO 084-08-000-00, one lot of each product should have been included in the long term stability study each year, and that in fact the firm had manufactured lots of Manzanilla Sophia 0.1% in 2013 and 2015, and lots of Nazil Ofteno 0.02% in 2013. Ms. Alcalá indicated that they will include in the stability program for 2015 the next lot of Manzanilla Sophia 0.1% only, because Nazil Ofteno 0.02% is no longer manufactured by the firm since 2014. There were neither investigations nor justifications documenting the reason why these products were not included in the annual stability program for 2013 and Manzanilla Sophia in 2015. Exhibit APZ1 is the annual stability program for 2015 where there is no lot included for Manzanilla Sophia 0.1% although one lot of this product has been manufactured during this year.

- 2. Your firm failed to test containers and closures for conformity with all written procedures and specifications. Specifically, tests for inserts and closures used during packaging operations of Manzanilla Sophia 0.1% lot number 4013510 performed on March 24, 2015 were actually concluded two months after, precisely in May 2015. (APZ)**

I reviewed firm's Certificate of Analysis (CoA's) for container and closure components used in the manufacture of Manzanilla Sophia 0.1% lot number 4013510 and Nazil Ofteno 0.02% lot number 4011267, along with the corresponding analytical data. The review disclosed that the CoA's of these materials were approved before the actual completion of the tests established in the corresponding specifications. These dates are presented in the following table:

| Material                           | Lot number                      | Analysis date | CoA approval date |
|------------------------------------|---------------------------------|---------------|-------------------|
| Bottle 15 ml irradiated Nazil      | 3014818                         | 01/2013       | 05/12/2012        |
| Insert irradiated Nazil            | 3014983                         | 03/2013       | 02/06/2013        |
| White cap irradiated Nazil         | 3015143                         | 02/2014       | 04/16/2013        |
| Bottle 15 ml irradiated Manzanilla | 3018582 analyzed as lot 3018631 | 07/2015       | 11/28/2014        |
| Insert irradiated Manzanilla       | 3018555                         | 05/2015       | 11/11/2014        |
| White cap irradiated Manzanilla    | 3018634                         | 05/2015       | 11/28/2014        |

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actions that will be taken to address the deviations cited on the FDA-483.

I informed the firm's officers that the items listed on the FDA-483 were in our opinion deviations from the drug regulations and that it was not an all-inclusive list. I also informed that it is the firm's responsibility to evaluate all of their systems to determine compliance with cGMP regulations. I encouraged firm's management to respond the FDA-483 and send the response letter to the FDA/CDER contact listed at the top of the FDA-483 form within 15 working days. I further stated that CDER has the final decision and authority regarding these observations and for the final classification of the inspection.

At the conclusion of the inspection, I thanked the firm's personnel for their cooperation during the EI. No further comments were made and the inspection was concluded.

## **SAMPLES COLLECTED**

No physical samples of finished product were collected during this EI. Specimens of labels for Manzanilla Sophia sterile ophthalmic solution were collected and attached as Exhibit 17 of this EIR.

## **VOLUNTARY CORRECTIONS**

This is the first FDA inspection to this site.

## **EXHIBITS COLLECTED (RNN)**

During the course of the inspection, we collected copies of records related to different operations of the firm. Exhibits were mostly provided by Mr. Rafael Castañeda, Quality Assurance Manager or Mrs. Alicia Morfin, Compliance Manager. These copies were collected at the firm's manufacturing facilities in Zapopan, State of Jalisco, México during the course of the EI. Copies provided had been made on paper stamped with "\*\*\*\*LABORATORIOS SOPHIA, S.A. de C.V.\*\*\*COPIA\*\*\*DE REFERENCIA\*\*\*DOCUMENTACION\*\*\*\*" or "\*\*\*\*USO DE\*\*\*REFERENCIA\*\*\*\*" in blue ink. We identified all documents included as exhibits and are attached to this EIR in the same order.

### **Exhibits collected by Investigator Rafael Nevárez (RNN):**

|           |                                                                                                                               |
|-----------|-------------------------------------------------------------------------------------------------------------------------------|
| Exhibit 1 | CDER Direct Electronic Submission documenting that Nazil Ofteno Ophthalmic Drops NDC 57619-300 Date of Marketing end Date was |
|-----------|-------------------------------------------------------------------------------------------------------------------------------|

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|            |                                                                                                                      |
|------------|----------------------------------------------------------------------------------------------------------------------|
|            | 04/29/2015.                                                                                                          |
| Exhibit 2  | List of products manufactured by Laboratorios Sophia, S.A. de C.V. exported to the US during the period 2011 – 2014. |
| Exhibit 3  | Laboratorios Sophia, S.A. de C.V. corporate office organizational chart.                                             |
| Exhibit 4  | Laboratorios Sophia, S.A. de C.V. site plan.                                                                         |
| Exhibit 5  | Laboratorios Sophia, S.A. de C.V. Quality organizational chart.                                                      |
| Exhibit 6  | Laboratorios Sophia, S.A. de C.V. Operations organizational chart.                                                   |
| Exhibit 7  | Laboratorios Sophia, S.A. de C.V. second level site plan.                                                            |
| Exhibit 8  | Laboratorios Sophia, S.A. de C.V. Line -1 HEPA filters diagram.                                                      |
| Exhibit 9  | Laboratorios Sophia, S.A. de C.V. Line -1 pressure and laminar flow diagram.                                         |
| Exhibit 10 | Ophthalmic Area HVAC System Description.                                                                             |
| Exhibit 11 | Firm's Purified and Water For Injection System plan.                                                                 |
| Exhibit 12 | Laboratorios Sophia, S.A. de C.V. Production Unit organizational chart.                                              |
| Exhibit 13 | Manufacturing Flow Chart for Ophthalmic Products.                                                                    |
| Exhibit 14 | Laboratorios Sophia, S.A. de C.V. Planning Unit organizational chart.                                                |
| Exhibit 15 | Laboratorios Sophia S.A. de C.V. Quality Control Unit organizational chart.                                          |
| Exhibit 16 | Laboratorios Sophia S.A. de C.V. Analytical Control Unit organizational chart.                                       |
| Exhibit 17 | Label specimens for Manzanilla Sophia.                                                                               |

**Exhibits collected by Regulatory Analyst Ana Patricia Pineda (APZ):**

|       |                                                                                                                                                |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------|
| APZ 1 | Annual stability program for 2015.                                                                                                             |
| APZ 2 | CoA of the Manzanilla Sophia lot number 4013510.                                                                                               |
| APZ 3 | CoA's and analytical report for the containers and closures used to package Manzanilla Sophia lot number 4013510.                              |
| APZ 4 | Water sampling program established in the SOP "Water sampling in the treatment plant, distribution network and pure steam condensates" PNO-SD- |

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|                            |
|----------------------------|
| 0451 effective 08/24/2015. |
|----------------------------|

## **ATTACHMENTS**

1. FDA-483 issued on 08/28/2015.
2. Facsimile Coversheet to the FDA issued on 08/31/2015.

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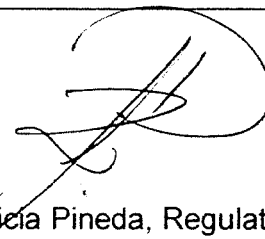
El End:

08/28/2015

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Rafael Nevarez Nieves, Investigator



Ana Patricia Pineda, Regulatory Analyst