DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration CDER/OC/DMPQ/ICT 10903 New Hampshire Avenue Bldg. 51, Room 4234 Silver Spring, MD 20993 Phone: 1-301-796-3206; email: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	03/13-17/2017
	FEI NUMBER 3002807208

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Guy Villax, Chief Executive

FIRM NAME	STREET ADDRESS
Hovione Farmaciencia SA	Quinta S. Pedro Sete Casas 2674 506
CITY, STATE AND ZIP CODE Loures, Portugal	TYPE OF ESTABLISHMENT INSPECTED API Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1 (Quality System)

The responsibilities and procedures applicable to the quality control unit are not in writing and/or fully followed.

Specifically,

a. Our review of your firm's commercial trending of deviations revealed the following:

In 2015 your firm generated a total of [redacted] deviations, where [redacted] of them were related to human errors

In 2016 your firm generated a total of [redacted] deviations, where [redacted] of them were related to human errors

Your firm's corrective actions were not adequate to prevent the re-occurrence of the deviations

b. Your firm's recall procedure # HQ.CCO.COP030.1.EN is inadequate, because it does not represent an actual recall. It is limited to verify products sent and the contact information of customers.

OBSERVATION 2 (Quality System)

Written procedures are not established/ followed for the OOS and deviation investigations, cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

a. Your firm's SOP HQ.CCO.COP014.11.EP, titled "Deviation Records" is deficient due to:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	D Shaheen Laura Fontan	Deyaa Shaheen, Investigator Laura Fontan, Consumer Safety Officer	03/17/2017

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• The procedure contains no instruction on how to determine if the deviation has occurred before as required by step 7 of the deviation investigation form

• Deviation investigation delay justification per step 5.3 is not consistently documented for investigations that require more than 30 days to complete

• The procedure provides no guidance for time line or performance of CAPA effectiveness

• The procedure provides no guidance on how to handle trends identified

b. Our review of your OOSs revealed that the following OOS [redacted] were past due 30 days and were not extended as per Section 5.3 and 5.6 of SOP #HQ.CCO.COP014.11.EP

c. The pallet truck scale, [redacted] used to verify raw material weights for the [redacted] process had no operating procedures or preventative maintenance plan.

d. SOP # HQ.GQ.IOP048.3.PO, Identification and Cleaning of Utensils and Pieces of Equipment was not followed. For example, in Building 15, a cage containing cleaning spray balls and assemblies and a tub full of [redacted] hoses, lacked status and identification.

OBSERVATION 3 (Laboratory System)

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

The liquid nitrogen distribution system used to supply manufacturing areas for use in manufacturing processes (direct product contact) is not qualified, routinely monitored or sampled to confirm identity, quality and purity.

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	D-Dn Shaheen Laura Fontan	Deyaa Shaheen, Investigator Laura Fontan, Consumer Safety Officer	03/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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Hovione Farmaciencia SA	Quinta S. Pedro Sete Casas 2674 506
CITY, STATE AND ZIP CODE Loures, Portugal	TYPE OF ESTABLISHMENT INSPECTED API Manufacturer

OBSERVATION 4 (Quality System)

Employees engaged in the manufacture, processing, packing, and holding of a drug product lack the training and experience required to perform their assigned functions.

Specifically,

Our review of your firm's record revealed that employees have not received GMP refresher training for more than two years as permitted per your firm's training SOP # HQ.CCO.COP007.6.EP

OBSERVATION 5 (Material System)

Separate and defined areas to prevent contamination or mix-ups are deficient regarding operations related to the holding of rejected raw materials and drug intermediates.

Specifically,

The following rejected materials were located in the receiving area of the Building 8 Warehouse with insufficient safeguards and separation:

- [redacted] code: 100337, batch: HQ00022
- [redacted] code:109909, batch: HQ00011
- [redacted] 04ST71046, batch:HQ00001

OBSERVATION 6 (Facility and Equipment)

Buildings used in the manufacturing and processing of a drug product are not maintained in a good state of repair.

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Hovione Farmaciencia SA	Quinta S. Pedro Sete Casas 2674 506
CITY, STATE AND ZIP CODE Loures, Portugal	TYPE OF ESTABLISHMENT INSPECTED API Manufacturer

Specifically,

On 03/13/2017, during the walkthrough in your facility we observed the following:

a. The zipper door curtain that separates the receiving area from the storage area, located in the ground floor, Building 8 [redacted] was not attached.

b. Gaps of various sizes on the bottom, right and left sides of the exit door located in the north side of Building 15, [redacted] near Reactor [redacted]

c. Gaps of various sizes on the bottom, right and left sides of the exit door located in the west side of Building 15, [redacted], near Reactor [redacted]. Additionally, the door was malfunctioning and did not completely close.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Deyaa Shaheen Laura Fontan	Deyaa Shaheen, Investigator Laura Fontan, Consumer Safety Officer	03/17/2017

Hovione

Hovione FarmaCiencia SA
Sete Casas
2674-506 Loures
Portugal

CMC17.005

Loures, 7th April 2017

Food and Drug Administration
CDER/OC/DMPQ/ICT
10903 New Hampshire Avenue
Building 51, Room 4234
Silver Spring, MD 20993
USA

To the attention of: CDER/OC/DMPQ/ICT

Re: Inspection carried out from 13th March to 17th March 2017 to the plant with FEI No.: 3002807208

Dear Sirs.

We refer to the inspection to our facilities in Sete Casas, Loures – Portugal, FEI No. 3002807208 performed on the dates mentioned above by your investigator Mr. Deyaa Shaheen and Ms. Laura Fontan.

This letter is our response to the observations that occurred during the inspection and were reported in the Form 483 issued which we consider a valued opportunity to improve our quality system.

The observations issued namely the ones related with deviations are driven by growth in size and complexity of operations during the last years. To mitigate this impact the organization had identified the need for a major re-structuring of the Quality Unit. The first changes had become effective in September 2016. During system evaluation, the need for better CAPA effectiveness was detected and triggered a continuous improvement activity (Nov 2016) to re-define procedures, operative mechanisms and establish clear definitions of roles and responsibilities.

Below is our commitment to proceed with specific changes to our quality system some identified before the inspection some others during the course of the evaluation of the observations received and that we feel are in accordance with the agency's expectations.

We commit to provide periodic feed-back on the action plan implementation status on 16th June, 16th of October 2017 and on 5th of January 2018.

OBSERVATION 1 - (Quality System)

The responsibilities and procedures applicable to the quality control unit are not in writing and/or fully followed. Specifically,

a. Our review of your firm's commercial trending of deviations revealed the following:
In 2015 your firm generated a total [redacted] deviations, where [redacted] were related to human errors.
In 2016 your firm generated a total [redacted] deviations, where [redacted] were related to human errors.
Your firm's corrective actions were not adequate to prevent the re-occurrence of the deviations.

b. Your firm's recall procedure #HQ.CCO.COP030.1.EN is inadequate, because it does not represent an actual recall. It is limited to verify products sent and the contact information of customers.

Hovione

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Food and Drug Administration

7th April 2017

Response to Observation #1a

We agree that the current deviation management system is not showing the adequate performance to prevent re-occurrences and trigger the right continuous improvement activities, this statement is also applicable to both observation #2a and #2b. We value the feedback from the FDA inspectors that confirms that we are in the correct direction with the ongoing improvement of our Quality structure and operative mechanism.

An increasing number of deviations has been opened in 2015 and 2016 with investigations concluding human error as root cause in many cases (1/3 of the cases). No improvement upon implementation of corrective actions could be detected over time.

Driven by growth in size and complexity of operations the organization had identified the need for a major re-structuring of the Quality Unit, the first phase of such changes became effective in September 2016. During system evaluation, the need for better CAPA effectiveness was detected and triggered a continuous improvement activity that started in November 2016 (Annex 1 – Charter on Deviation Flow project) to re-define procedures, operative mechanisms and establish clear definitions of roles and responsibilities. Additionally two pilot knowledge management systems were implemented to facilitate trending of deviations across all Hovione sites and identify re-occurrences globally through the use of advanced text searching of related documentation. Results of this innovative work were presented at the IFPAC 2017 in Bethesda earlier this February (see relevant information in Annex 2).

Improvement to the Deviation Management System is ongoing and has following objectives:

- Refine definitions of corrective and preventive actions considering re-occurrence related to the project, to other areas at site and to other manufacturing sites.
- Ensure criticality assessment of events to focus effort on critical aspects
- Trend deviations, root causes and CAPA effectiveness with a defined dashboard
- Institutionalize management oversight on performance dashboards (from Manufacturing Site and Corporate Quality Unit)
- Collect results on a corporate level to define continuous improvement strategy
- Establish systematic investigation procedures and train lead investigators.
- Implement quarterly management review of CAPA effectiveness
- Ensure deviation resulting in a human error as root cause need approval for closure by a QA Director/Head or delegate in peer level.

For the flagged item the corrective actions in the years 2015 and 2016 were in essence ineffective and it is clear that the methods, procedures, systems, etc. may have not been improved sufficiently to mitigate the errors and lead to a reduction of the number of deviations.

The following actions will be taken to understand better and to de-risk the current situation:

- Creation of a dedicated function to lead the cross-functional task force (Quality Performance Director)
- Risk based action plan for open deviations
- Re-evaluation of all deviations from 2016 with unassigned root cause, or human error to identify common risk areas → risk based action plan to establish global preventative mechanisms to minimize re-occurrence. Any potential impact on product Quality will result in an immediate action.
- Management review of the progress
- Training and oversight to ensure that every deviation (including OOS) that is not closed within 30 days needs written justification and definition of realistic closing dates.

The CAPA #56207 has been opened to manage the above mentioned issues.

Obs. 1a) Action Plan

Observation #1a: Corrective action plan	**ID#**	**Status**	**Implementation Date**
1.a.1. Improvement of current Deviation Management System, specifically (but not limited to): i) Implementation and standardization of investigation methodologies. This will improve the investigation efforts and conclusions; ii) Improve definition of recurrence and implementation of a tool that will ease the verification of re-occurrence. This will allow improvement in identifying re-occurrence and in the root-cause analysis, solutions effectiveness evaluation and crosswise implementation; iii) Improve the CAPAs, solutions, definition (the effectiveness criteria and expected outcome must be clear the, and better understanding of the transversal potential of the CAPAs is required); iv) Implement a monitoring system (including trend analysis) to continuous evaluate the deviation system performance	Charter 01/2017 (see Annex 1)	Under implementation	Gate reviews by: 16 June 2017 16 Oct. 2017 5.Jan 2018
1.a.2. Re-evaluation of 2016 CAPAs which concluded in human error as root-cause. Identify patterns in the observation, check for re-occurrences within and cross-facility and establish a continuous improvement plan with defined actions and due dates.	CAPA #56207	Not started	16.Jun.2017
1.a.3. Revise the HQ.CCO.COP014 to refine definitions, provide more detail on investigation mechanisms, root cause analysis, trend evaluations and CAPA effectiveness evaluation according to the outcome of 1.a.1 activities	CAPA #56323	Not started	16.Jun.2017
1.a.4 Training to all staff involved in deviations and OOS (minimally but not limited to Manufacturing, QC, QA), on the updated procedure and improved methodologies namely with respect to the 30 day limit to close or justify an extension period for closure	CAPA #56350	Not started	16.Oct.2017

Obs.1b. Your firm's recall procedure #HQ.CCO.COP030.1.EN is inadequate, because it does not represent an actual recall. It is limited to verify products sent and the contact information of customers.

Response to Observation #1b

Hovione HQ.CCO.COP030.1.EN describes the procedure to be followed when Hovione detects that a product already released to customers does not conform to its specification, or presents problems that may affect the quality/safety/stability of the final product or there is a discrepancy in the inventories. As per the procedure any of the above cases will trigger the issuance of a deviation within one (1) working day and an investigation coordinated by quality unit (QAU). If the outcome of the investigation shows that there is a potential health hazard QAU and Regulatory Affairs department shall determine if the recall is justified. In this case

customer(s) that have received the material are informed within one (1) working day. The investigation report must be provided to obtain their assessment and confirmation that a health hazard exists. Customer is requested to inform Hovione of the product status and whether or not it was already released for distribution to the market. The recall from the market is then a joint decision between customer(s) that hold a marketing authorization and Hovione. How to proceed is agreed and recorded in the deviation report, this also records all related actions taken (corrective and preventive action) including how the product should be handled after being received at Hovione.

We understand from the discussion with the investigators during the inspection that this observation does not relate to the recall procedure defined in the COP, but relates to a deficiency in our mock-recall procedure which does not require obtaining a response from the receiving site(s) within a defined time frame.

Indeed the mock recall only tests the capability to retrieve following information from the Hovione systems: Receiving site(s) of the identified batches numbers, when were they delivered and to whom and to where, which quantity was delivered and does the amount produced and packaged align with Batch Production Record documentation.

It is important to note that that Hovione produces both APIs and Intermediate Drug Products, but does not produce final forms of drug products – Medicinal Products. We are not the holder of any marketing authorization.

Hovione acknowledges that currently the procedure is limited to verify that product was sent, and only includes contact information of customers. This Mock Recall exercise is being performed since 2013 and does indeed not demand active feedback from the customer which woud be a good test of the effectiveness of the recall procedure.

Hovione agrees on the need and benefit that our mock recall procedure should be expanded to ensure that we obtain conclusive feedback from the receiving site(s) in order to ensure effectiveness of the procedure. We had tried to do this in the past but clients had been reluctant to collaborate. There was an insufficient commitment from customers to be included in such expanded mock recall ended procedure into joint agreements.

We take the observation to be the current status of the agency's expectations and shall communicate this to our clients. In this light we now expect clients to be cooperative in performing mock recalls and that Quality Agreements shall updated to reflect such mock recall cooperation commitments.

The procedure HQ.CCO.COP030.1.EN was under revision at the time of the inspection. For the reasons detailed above we have extended the scope of change to include the need of recording feedback from the receiving site into the procedure. The revision of the procedure is governed by the change control # 6927. The new version of the procedure, the updated Mock Recall protocol, a new Recall protocol and a revision of the Quality Agreement Template have been approved see Annex 3.

A controlled roll-out will include training to all relevant areas to ensure aligned application at all of our manufacturing sites.

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Obs. 1.b). Action plan

Observation #1b: Corrective action plan	ID#	Status	Implementation Date
1.b.1 - Update the Mock Recall protocol to include the communication with the clients and expectations on their response	PdA # 6927	Completed	07.Apr.2017
1.b.2 - Recall protocol to be issued including the communication with the clients	PdA #6927	Completed	07.Apr.2017
1.b.3 - HQ.CCO.COP030 "Recall Procedure" to be revised accordingly	PdA #6927	Completed	07.Apr.2017
1.b.4 - Update the Hovione Quality Agreement template to include the availability for client participation on a Mock Recall with Hovione, whenever requested (see Annex 3)	CAPA #56205	Completed	07.Apr.2017
1.b.6 - Execute Mock Recall (following the updated procedure) with at least one client	CAPA# 56206	Not started	16 June 2017
1.b.7 – a letter will be sent to all customers with whom we have a Quality Agreement in place notifying them that their cooperation in a Mock Recall exercise is a requirement from FDA inspection and a plan for review of the Quality Agreement is needed	CAPA#56243	Not started	16 June 2017
1.b.8 – Training of relevant areas on changes in procedures in all sites	CAPA#56244	Not started	31.May.2017

OBSERVATION 2 - (Quality System)

Written procedures are not established/ followed for the OOS and deviation investigations, cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.
Specifically,

a. Your firm's SOP HQ CCO.COP014.11.EP, titled "Deviation Records" is deficient due to:

- *The procedure contains no instruction on how to determine if the deviation has occurred before as required by step 7 of the deviation investigation form*
- *Deviation investigation delay justification per step 5.3 is not consistently documented for investigations that require more than 30 days to complete*
- *The procedure provides no guidance for time line or performance of CAPA effectiveness*
- *The procedure provides no guidance on how to handle trends identified*

b. Our review of your OOSs revealed that the following OOS [redacted] were past due 30 days and were not extended as per Section 5.3 and 5.6 of SOP #HQ.CCO.COP014.11.EP

c. The pallet truck scale, Equipment ID: BA2001, used to verify raw material weights for the [redacted] process had no operating procedures or preventative maintenance plan.

d. SOP# HQ.GQ.IOP048.3.PO, Identification and Cleaning of Utensils and Pieces of Equipment was not followed. For example, in Building 15, a cage containing cleaning spray balls and assemblies and a tub full of [redacted] hoses, lacked status and identification.

Response to Observations #2a and #2b

Elements described in observation #2a and 2#b are related with the deficiencies in procedure *HQ.CCO.COP014.11.EP – Deviation Records* - that is insufficiently clear by not being specific enough about the following:

i) The definition of deviation re-occurrence is not to be understood limited to product code level (within the same production line) but applies to all other product code levels or another production line in any of Hovione's other manufacturing sites;
ii) required actions (ie noting rationale) for extending of deviation for longer than 30 days in every instance;
iii) timelines for checking CAPA effectiveness and;
iv) defined reaction mechanisms based on trending results.

We accept the observation, and agree that the related corrective actions are desirable as they drive improvement to our Quality system. All 4 items mentioned above and call for correction are also addressed by the corrective action plan in the response to observation #1a. Our procedures will be revised to comply with requirements summarized above.

As explained in the observation #1a, because of the growth in size and in the complexity of our operations the organization had already identified the need for a major re-structuring of our Quality Unit. Prior to September 2016 Quality Assurance was split into two quality assurance areas: QA for Commercial products and QA for Development products, each reporting to different Vice-Presidents (manufacturing and R&D respectively) with a compliance area reporting to the CEO. In that organization each Quality Assurance Technical Expert was responsible for specific product lines / projects and the concern for the identification of re-occurrences was, mistakenly, limited to finding re-ocurrences within in his/her area of responsibility. Also the organization did not have a transversal function dedicated to look across production lines and across the sites. Similarly absent powerful IT tools it would have been difficult to efficiently scan across all production lines to identify clustering of deviations.

The new organization that has become effective on 3rd of April 2017 is not only addressing this issue but has been charged to address it. The new organization includes:

- Clear definition of areas of responsibility (by production line/project, as well as transversally) and that re-occurrence is understood to be across all Hovione sites
- Escalation mechanism to the Quality site responsibles, and directly up to the VP Quality, and eventually to Hovione's Managament Board.
- Cross-site governance bodies via Quality Committes are being established to promote alignement and sharing of best practises.
- Periodic management meetings to review the status of deviations and effectiveness of CAPAs are being established to be able to set focus and allocate ressources to critical issues.

As described in observation #1a improvement to Deviation Management system is ongoing.

As identified for deviations classified as OOS corrective actions in the years 2015 and 2016 have not proven to be fully effective. The following actions (same as per #1a) will be taken to understand better and to de-risk the current situation:

- Creation of a dedicated function to lead the cross-functional task force (Quality Performance Director)
- Risk based action plan for open deviations
- Re-evaluation of all 2016 deviations with unassigned root cause, or human error to identify common risk areas → risk based action plan to establish global preventative mechanisms to minimize re-occurrence. Any potential impact on product Quality will result in an immediate action.
- Management review of the progress
- Training and oversight to ensure that every deviation (including OOS) that is not closed within 30 days needs written justification and definition of realistic closing dates.

The CAPA #56207 to correct the current situation will cover both deviations and OOSs.

Obs. 2a) and 2b) Action plan

Observation #2a and #2b: Corrective action plan	**ID#**	**Status**	**Implementation Date**
2.a.b.1 - Revision of HQ.CCO.COP014.11.EP procedure (the same as in the Action Plan 1.a.3.)	CAPA#56323	Not started	16.Jun.2017
2.a.b.2 - Training to all staff involved in deviations and OOS (minimally but not limited to Manufacturing, QC, QA), on the updated procedure and improved methodologies namely with respect to the 30 day limit to close or justify an extension period for closure.	CAPA#56350	Not started	16.October.2017
2.a.b.3 - Re-evaluation of past-due OOSs. Determination of criticality, and definition of immediate action in case of product quality impact. Definition of realistic extension dates (the same as in the Action Plan 1.a.4.)	CAPA #56207	Not started	16.Jun.2017

c. *The pallet truck scale, Equipment ID: BA2001, used to verify raw material weights for the* [redacted] *process had no operating procedures or preventative maintenance plan.*

Response to Observation #2c

The pallet truck scale BA2001 is dedicated to Building 15 operations due to the size of the building and the amount of product handled there. The scale is calibrated according to the procedure in place HQ.CCO.COP010 – Calibrations, and is included in the calibration schedule of the site instruments which is managed through SAP system.

We acknowledge that besides the calibration plan no other maintenance activity plan was defined for this equipment. Any maintenance requirements are defined only at the time of the calibration / qualification activities in case the precision of the equipment falls outside the error limit. The assumption being that if the equipment had any issue beyond failing the error limit, it would be identified during calibration and this would trigger the investigation and correction (e.g. tires with insufficient air pressure).

We listened to the inspectors' concern and after reviewing the respective documentation we acknowledge that a preventive maintenance (PM) further strengthens the control strategy applied to this equipment. During the course of the inspection a preventive maintenance program was included in the SAP system for this, and all other similar pallet truck scales in use at the site (see Annex 4).

Recognizing the importance of this aspect, and to prevent re-occurrence of similar situations, we have now defined the appropriate criteria that will require a PM plan to be established for any equipment that meets such criteria. This requires an update to the maintenance procedure (HQ.MC.IOP013.A1.1.PO) and to the equipment qualification form templates.
This procedure will be deployed to all the other Hovione sites which were all informed on the current observation and the associated corrective actions.

Obs. 2c) Action plan

Observation #2c: Corrective action plan	**ID#**	**Status**	**Implementation Date**
2.c.1 – Inclusion of PM in SAP system for the pallet truck scale BA2001	Immediate action during inspection	Completed	16.Mar.2107
2.c.2 – Inclusion of PM in SAP system for all remaining pallet truck scales used at the site	Immediate action during inspection	Completed	16.Mar.2107
2.c.3 - Revise maintenance procedure HQ.MC.IOP013.A1.1.PO with definitions of the criteria for setting up a Preventive Maintenance Plan for any equipment	CAPA#56211	In progress	28.Apr.2017
2.c.4 - Update equipment qualification forms to include an assessment for the inclusion of PM	CAPA#56212	In progress	28.Apr.2017

d. SOP# HQ.GQ.IOP048.3.PO, Identification and Cleaning of Utensils and Pieces of Equipment was not followed. For example, in Building 15, a cage containing cleaning spray balls and assemblies and a tub full of [redacted] hoses, lacked status and identification.

Response to Observation #2d
The procedure HQ.GQ.IOP048.3.PO – "Identification and Cleaning of Utensils and Pieces of Equipment" in place at the inspected site is applicable to all utensils and equipment spare parts new or in use that are, or may be in contact with the product – *Section 2 Scope*.

The procedure also states in "*Section 5.1 Type of utensils and identification*" that the utensils (spatulas, cups, spray balls, hoses, etc.) should be dedicated to the production area and/or the product line and whenever possible each utensil is clearly identified by the initials of the area/product. If not possible on the utensil itself unequivocally identification of the area of use should be made possible by any other mean. Hoses used in manufacturing processes are cleaned in accordance to the cleaning procedure in force and preferentially together with the main equipment.

In *Section 5.3. Identification of cleaning status and maintenance* it is stated that after the visual verification of the cleanliness and dried status of the utensils they should be:

- Protected with a clean plastic bag which should at least cover the area of the utensil that is in contact with the product or can be stored in a dedicated closed closet or closed box. In this case the cleaning status of the utensils can be placed in the cabinet door or on the box as an alternative to placing it on each utensil.

As described in the latter, the hoses used for the [redacted] process were inside a box with the cleaning status identification marked on the outside of the box. Additionally the hoses were identified with the product code (PT01). This identification however deviated from the defined way because the equipment was new in the area, otherwise the current procedure was followed:

- During the inspection the hoses were duly found to be appropriately marked as dedicated to PT01 with the ends protected with clamps.

The utensils and hoses in use in all other Manufacturing and Pilot plant areas were checked to make sure that all were following the procedure in place. All others were found correctly identified. We acknowledge that our current system has a weakness, indeed there are some items that if removed from the box could loose the identification of their cleaning status.

The procedure was reviewed and adapted to include clear guidance on the identification process and rules related to assignment of the code, how to clean, store and use the auxiliary equipment, namely hoses. The sole reliance on a cleaning status written on a box (a bundle of separate pieces of equipment or utensils) will not longer be permitted – each item will have to have its own specific cleaning status. Auxiliray equipment that is removed from the area/containment that defines its cleaning state and is not used immediately will be categorizes by default as "not clean". Alternatively critical equipment can have unique identifiers (such as bar codes) with their cleaning status managed via the SAP system and making it retrievable at any time.

All relevant areas will be trainined on the revised procedure.

All sites were informed about the observation and measures are being taken whenever similar situations have been identified.

Obs 2d) Action plan

Observation #2d: Corrective action plan	**ID#**	**Status**	**Implementation Date**
2.d.1 – Correct the situation of the PT01 hoses: the hoses were dully marked as dedicated to PT01 and the ends covered with a plastic bag and labelled as "Cleaned and inspected"	Immediate action during inspection	Completed	16.Mar.2017
2.d.2 – Assess and correct if needed, labelling of the remaining hoses used at the site	Immediate action during inspection	Completed	30.Mar.2017
2.d.3 - Update procedure HQ.GQ.IOP048 to include clear guidance on the identification, cleaning, use, labelling, verifications	Immediate action during inspection	Completed	16.Mar.2017
2.d.4 – Training to all manufacturing areas on the new revised procedure HQ.GQ.IOP048 will be provided	CAPA#56327	Ongoing	28.Apr.2017
2.d.5 – All sites will update if need there own procedure, and will prepare an implementation plan	CAPA# 56436	Ongoing	28.Apr.2017

OBSERVATION 3 - (Laboratory System)

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,
The liquid nitrogen distribution system used to supply manufacturing areas for use in manufacturing processes (Direct product contact) is not qualified, routinely monitored or sampled to confirm identity, quality and purity.

Response to Observation #3

Liquid Nitrogen is received in trucks and discharged to Hovione tank directly by supplier – AIR Liquide. The supplier is a qualified supplier as per Hovione internal procedure.
Following the changes in the Liquid Nitrogen distribution system across the plant on December 2015 it was decided to proceed with the qualification of the system. Some gaps were identified during the qualification activities and several actions were defined (see Annex 4. HQ.QSD.VMP089.0.EN). As shared with the inspection team, some of the actions were already implemented, others are still under implementation. The following activities are ongoing:

1) Introduce Nitrogen testing plan at each Point-of-Use
The nitrogen supplied at the point of use is no longer a liquid but a gas. It was decided to implement this control in accordance with the European Pharmacopeia (EP); US Pharmacopeia, National Formulary (NF) and ISO 8573.1:2010 for Total Oil Content (Hydrocarbons (CnHm)). This action was recorded at Hovione CAPA system with the reference CAPA #46354. Samples across the distribution system were defined, collected samples to be analised according to the USP and EP monographs and the results are under evaluation. Actions to correct/improve the system will be defined if required.

2) Liquid Nitrogen supplied to Hovione
The control of the Liquid Nitrogen received is currently based on a certificate of conformity received together with each tank truck load supplied.
As per the GMP guidelines on hazardous materials, a full analysis should be performed at appropriate intervals. This has been requested by Quality Assurance. Two CAPAs were issued in February 2016 to solve this issue:
   - CAPA #46353 requests the full analysis at appropriate intervals (due date: 30.May.2017);
   - Change Control form #6742 was issued and the Tasks #102610 and #101811 were opened requiring the Outsourcing of a Lab for Nitrogen purity testing and associated Supplier Qualification (expected completion date: 30.Apr.2017).

A 3rd party laboratory with the required capabilities has been identified and is currently in the process to be qualified per Hovione supplier qualification procedure.

The complete qualification of the Liquid Nitrogen system is planned to be completed when the above tasks are closed and approved by Hovione Qualification & Validation department (see qualification plan HQ.QSP.VMP089.0.EN at Annex 5).

Obs. 3 Action plan

Observation #3: Corrective action plan	**ID#**	**Status**	**Implementation Date**
3.1 - Implementation of full analysis at appropriate intervals	CAPA #46353	Under Implementation	30.May.2017
3.2 - To qualify an external laboratory to perform the purity testing	Change Control request #6742	Under Implementation	30.Apr.2017

OBSERVATION 4 - (Quality System)

Employees engaged in the manufacture, processing, packing, and holding of a drug product lack the training and experience required to perform their assigned functions.

Specifically,
Our review of your firm's record revealed that employees have not received GMP refresher training for more than two years as permitted per your firm's training SOP# HQ.CCO.COP007.6.EP

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7th April 2017

Response to Observation #4

As per Hovione corporate procedure *HQ.CCO.COP007.A1.4.EN* – Training - Annex A1: *HQ Training program implementation details* (Annex 6) the GMP refresh sessions at Loures site are performed at maximum every 3 years in the 3 main operational areas: manufacturing, warehouse and quality control.

We accept that this procedure is not in line with current industry practice. Our other sites already have a shorter period for "GMP refreshing".

Although not evidenced by attendance records, we shared evidence with the inspectors of a sustained effort to constantly refresh the minds of all personnel involved in GMP operations of the importance of GMP. In Annex 7 we provide a copy of a summary describing the Hovione approach to continuously improve GMP awareness and training at the manufacturing lines and provide content oversight of material that has been used since October 2010 for this purpose.

Because we realize the importance that all the employees that work in GMP operations should be constantly reminded as to the importance of working with good manufacturing practices we instituted the "GMP 1st minute" initiative 6 years ago. On a weekly basis Quality Assurance issues 2 different GMP awareness subjects per week each in a one slide format. This continuously calls the attention of all operational areas on the correct way how to execute GMP operations. The "GMP 1st Minute" training has been occurring in Loures every Friday since October 2010. During this exercise the two GMP examples picked for that week, and reflected in the 2 slides, are explained to the Team Leaders and Technical staff. In cascade fashion, they will in turn use such slides to explain the topics to all their staff during the following week – this training moment occurs at the "Top 5" meeting (this is a structured meeting to manage the change of shift and ensure good hand-over of on-going matters between teams). If required the subject matter of the training can be revisited more than once per year. Examples of focus areas are the following -but not limited to-:

- How to correct a manual record entry in a batch production record;
- Data integrity: definition of each of the ALCOA letters;
- How to handle biocontainers;
- What to check before using a scale;

Please see Annex 7 that shows the variety of topics that have been covered during "GMP 1st Minute" sessions.

The "GMP 1st Minute" is exactky the right kind of activity that helps building a quality culture, however since we have not in the past recorded what operators or analysts attended the "GMP 1st Minute" from a compliance perspective it is as if this training had never happened. Our decision is to continue doing the "GMP 1st Minute" and to find ways that allow us to record the name, date, time and location of the individual's attendance of what "GMP 1st Minute" sessions as identified by the specific QA issues slide.

Hovione accepts the observation that the current maximum interval of GMP refresh training is inadequate.

Improvements to the current GMP training program had been initiated already during the previous year focusing on the following objectives *(but not limited to)*:

- Improve attendance of GMP training;
- Increase GMP refresher training frequency (provide at least one GMP training per employee each year, for the personnel directly involved in GMP related activities (e.g Manufacturing and Quality Units).

Obs. 4. Action plan

Observation #4: Corrective action plan	ID#	Status	Implementation Date
4.1 - Implementation of an improved corporate GMP training program, that will increase the refresher GMP training frequency to at least once per year	Change Control Request #6626	Under Implementation	16.Jun.2017
4.2 - Review the training procedure CCO.COP007-A1 to include the new corporate GMP training program details for the Loures Site	Change Control Request #6626	Under Implementation	16.Jun.2017

OBSERVATION 5 - (Material System)

Separate and defined areas to prevent contamination or mix-ups are deficient regarding operations related to the holding of rejected raw materials and drug intermediates.

Specifically,
The following rejected materials were located in the receiving area of the Building 8 Warehouse with insufficient safeguards and separation:

- [redacted] *code: 100337, batch: HQ00022*
- [redacted] *code: 109909, batch: HQ00011*
- [redacted] *code: 04ST71046, batch: HQ00001*

Response to Observation #5

The three rejected materials mentioned in this observation were two raw materials (100337 and 109909) and one intermediate API product (04ST71046) which were located in the rejected area in warehouse building 8 reception zone. Materials carried clear identification and were placed inside closed and controlled containers that were sealed with a numbered tag tie; the tag tie number was recorded in a specific record form to ensure traceability of the box's content.

The access to warehouse building 8 is restricted to warehouse staff and security staff (controlled by card access). Additionally, in all the warehouse areas (including building 8), the material status is controlled by SAP system. This does not allow the delivery/use of rejected materials (unless duly authorized and approved by Quality Assurance in the SAP system, for very specific situations).

For finished product materials, the rejected materials are placed in the rejected area inside the finished products warehouse (physically closed and access restricted) located at Lumiar.

Hovione acknowledges that the area in which the boxes were located was not optimal, yet controls that prevent the misuse of the rejected materials where in place. We agree with the opinion of the inspectors to better address the segregation and safeguards of the rejected raw materials and intermediate products. We recognize the importance that management cannot send any signal that underestimates the concern with rejected product. A reasonably sized labeled, segregated and locked area has been installed in the warehouse B8 first floor (in the raw materials storage area) to place all rejected/returned raw materials and intermediates. The three referred rejected materials were moved to this area during the course of the inspection.

Fig. 1 - Lumiar Warehouse - Rejected products area

Fig 2 – Loures Warehouse – Rejected materials area

No further actions were identified for other corrections related with this observation at the Loures site.
The other sites were informed and confirmed that all rejected materials are duly segregate and stored in locked cages (Annex 8 – photos of the other sites storage rejection area)

Obs. 5. Action plan

Observation #5: Corrective action plan	**ID#**	**Status**	**Implementation Date**
5.1 – Create a segregated and locked area in the warehouse B8 raw materials storage area to place all rejected/returned/recalled raw materials and intermediates	Immediate action during inspection	Completed	16.Mar.2017
5.2 – Place the three rejected materials referred in this observation in the new area (5.1)	Immediate action during inspection	Completed	16.Mar.2017

OBSERVATION 6 - (Facility and Equipment)

Buildings used in the manufacturing and processing of a drug product are not maintained in a good state of repair.
Specifically,
On 03/13/2017, during the walkthrough in your facility we observed the following:

a. *The zipper door curtain that separates the receiving area from the storage area, located in the ground floor, Building 8 Warehouse was not attached.*
b. *Gaps of various sizes on the bottom, right and left sides of the exit door located in the north side of Building 15, fifth floor, near Reactor #RV2512.*

c. *Gaps of various sizes on the bottom, right and left sides of the exit door located in the west side of Building 15, fourth floor, near Reactor #RV4010. Additionally, the door was malfunctioning and did not completely close.*

Response to Observation #6
We agree with the opinion of the inspectors that all manufacturing buildings should be kept in a good state of repair, as per GMPs, guidelines and regulations and stated by Hovione internal procedure CCO.COP008 – Building, facilities and utilities: "*Operational buildings should be properly maintained and repaired, and kept in a clean condition*".

As immediate action, all the three doors identified were corrected during the course of the inspection, all other doors from the remaining manufacturing buildings were assessed. In order to prevent similar situations, we will include a periodic verification of all doors, windows and piping entrance of the manufacturing buildings (under the preventive maintenance periodic activities).

All Hovione sites were informed of the Form 483 and requested to assess the status in their own sites related to the same or similar situations.

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Obs. 6. Action plan

Observation #6: Corrective action plan	**ID#**	**Status**	**Implementation Date**
6.1 – Repair the warehouse zipper door	Immediate action during inspection	Completed	16.Mar.2017
6.2 – Seal exit door located in the north side of Building 15, fifth floor, near Reactor #RV2512	Immediate action during inspection	Completed	16.Mar.2017
6.3 – Seal exit door located in the west side of Building 15, fourth floor, near Reactor #RV4010	Immediate action during inspection	Completed	16.Mar.2017
6.4 – Check all doors from Loures Site operational areas building (production areas, warehouse, laboratories, etc.) and if possible correct as need	CAPA #56343	Completed	07.Apr.2017
6.5 - Prepare a list of all identified doors, windows and piping entrance per operational areas building (production areas, warehouse, laboratories, etc.), requiring intervention with location and status for SC site – Annex 9	CAPA #56344	Completed	07.Apr.2017
6.6 – Include in SAP PM the verification of the status of repair of doors and windows for all the site operational areas buildings (production areas, warehouse, laboratories, etc) – Annex 10	CAPA #56347	Completed	07.Apr.2017
6.7 – All sites to perform a walkthrough to identify improvements. A list with the improvements required if applicable and a correction plan to be issued.	CAPA #56438	ongoing	28.Apr.2017
6.8 – Implementation of periodic walkthrough menchanisms to ensure continuous maintenance of sites	CAPA #56441	ongoing	28.Apr.2017

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7th April 2017

We trust this response adequately addresses the observations raised during the inspection. However, please do not hesitate to contact us should you require any further clarification or should you wish to receive copies of other documentation mentioned or of evidence of compliance with commitments set out above.

We plan to have all actions defined above completed by 16th October 2017 with the exception of the verification/control phase of the deviation management system improvement project (see action plan1.a.1). By nature of a verification phase we extended this activity up to 5th of January to be sure of sustainable effect.

Assuring you of our best regards, we remain

Yours sincerely,

Luisa Paulo
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7th April 2017

List of enclosures:

Annex ref:	Description	Cover letter page
Annex A	Action Plan revision 0	
Observation 1a		
Annex 1	Charter on Deviation Flow project	2
Annex 2	Knowledge Management (IFPAC 2017 presentation)	2
Observation 1b		
Annex 3	Recall Procedure HQ.CCO.COP030.2.EN Recall Protocol – HQ.QSD.RF1341 Mock Recall protocol – HQ.QSP.MP001 Hovione Quality Agreement template	4
Observation 2c		
Annex 4	Pallet Truck Scale – Preventive Maintenance Plan and the list of all Pallet Truck scale	7
Observation 3		
Annex 5	Nitrogen Qualification Plan – HQ.QSD.VMP089.0.EN	9
Observation 4		
Annex 6	HQ.CCO.COP007.A1.4.EN – HQ Training Program Implementation Plan	10
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Observation 5		
Annex 8	Rejection areas in all Hovione sites	13
Observation 6		
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Annex 10	SAP Maintenance plan for the doors and windows	13

Hovione

Hovione FarmaCiencia SA
Sete Casas
2674-506 Loures
Portugal

CMC17.006

Loures, 19th June 2017

Food and Drug Administration
CDER/OC/DMPQ/ICT
10903 New Hampshire Avenue
Building 51, Room 4234
Silver Spring, MD 20993
USA

To the attention of: CDER/OC/DMPQ/ICT

Re: Inspection carried out from 13th March to 17th March 2017 to the plant with FEI No.: 3002807208
June 2017 Gate Review

Dear Sirs.

We refer to our letter sent to your attention on the 7th April 2017 in response to the form 483 we received from your investigators Mr. Deyaa Shaheen and Ms. Laura Fontan on the 17th March 2017 inspection close meeting.

This letter is to provide you an updated status report on the action plan defined in above referenced letter. From the 19 actions described in the letter from 7th April 2017 and summarized in the Annex A of the same letter 17 had the target date of 16.Jun.2017 or earlier.
From the gate review performed as planned we are pleased to inform you that all 17 actions were implemented as planned. Only the 2 with later implementation date (maximum 5th January 2018) are yet ongoing due to their specificity and to implement a system over which we have a good control.

Below you can find a summary of what has been done and status.

OBSERVATION 1 - (Quality System) – Response #1a – Action Plan status

As referred in our letter dated April 7th, an improvement to the Deviation Management System is ongoing. The following objectives are already completed:

- Establish the definition of reoccurrence, corrective action, preventive action and effectiveness;
- Standardization of the description phase;
- Ensure risk assessment of events to prioritize effort on deviations with higher risk;
- Establish systematic investigation procedures, focused on root-cause analysis and adjusted to the level of complexity of the deviation;
- Definition of an action denominated as "reoccurrence evaluation" to be performed during the Investigation Procedure. In case of a deviation being a recurrence, it needs to be understand why did it recurred;
- Ensure deviation resulting in a human error as root cause are properly justified;
- The implementation of effectiveness criteria, that will guide the evaluation of effectiveness of the corrective actions;
- Establish a procedure to handle with corrective actions that were not effective;

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- Design a procedure to perform trend analysis related to the deviation system that promotes continuous improvement.

In order to implement the new Deviation Management System, the following complimentary projects of the program are being performed:

- Upgrade or replacement of the current electronic platform, user requirements are being defined and will be closed until 31st July;
- Training strategy is being defined with the support of an external entity;
- An operational plan is being developed in order to support the Deviation Management System to achieve:
  - Reduction of deviations;
  - Reduction of reoccurrence deviation rate;
  - Increase of corrective actions effectiveness;
  - Increase the rate of preventive actions.
  - No deviations or other proceedings related with deviations are out of due date"

The revision of the HQ.CCO.COP014 was planned following the action defined as 1.a.1. The revision of this procedure is completed (see new draft version attached as Annex 1.a.3.1). This is a high level procedure that is now under internal evaluation across all Hovione sites: i) to understand the impact on each site, ii) to define the next actions, iii) to help all sites to implement it and iv) to prepare the planned training sessions. Additionally a second procedure with more detail on how to handle deviations (how-to-do) was prepared and is currently under evaluation by all sites.

For the flagged item 1.a.2 related with the corrective actions in the years 2015 and 2016 which were in essence ineffective, the following actions were implemented:

- Creation of a dedicated function to lead the cross-functional task force (Quality Performance Director)
- Risk based action plan for open deviations
- Re-evaluation of all deviations from 2016 (Action plan 1.a.2) with assigned root cause as human error to identify common risk areas → risk based action plan to establish global preventative mechanisms to minimize re-occurrence. Any potential impact on product Quality will result in an immediate action.

To re-evaluate the 2016 deviations either with Human Error as root cause or past-due OOS (refer to Action plan 1.a.2 and 1.a.4 below) a team was defined with the purpose defined above. 209 (two hundred nine) deviations were reviewed and 2 (two) main categories were identified: Quality Control and Production/Operations (see Annex 1.a.2.1.)

Both categories were reviewed independently and the following conclusions were drawn:

a) Quality control deviations
In this group two sub-categories were identified "*Product Analysis*" and "*Environmental Control*" testing.
For the first sub-category (Product Analysis) two trends the deviations were observed when classified by type of failure and type of analysis: i) Execution and settings during release and stability testing and ii) LIMS/Evaluation data during IPC/intermediate analysis.
Basically the two trends are related with the different procedure followed for the two types of tests. In the IPC testing a peer review of all system settings and method conditions is performed prior to execution through the use of a check-list. No review of the system settings prior to execution is performed for release/stability tests as they have additional review strategies after testing. This may

contribute to increased opportunities of error (high probability). However the detectability of failure is high due to the final review of the analysis.

An improvement action was proposed by the team to implementation the "system settings review", prior execution. Priority was given to chromatography tests.
The need to reduce the number of deviations in IPC/intermediate have been already identified by the QC labs. Some improvements on the review process in QC laboratories are currently under implementation.

Regarding Environmental Control in manufacturing rooms the main cause identified is also related with operational execution, like poor sanitization or contamination during monitoring. The rooms in Building 1 are the ones with high number of reoccurrences (nine). The annual report on the environmental performance is under preparation and will summarize evaluation of all deviations. No additional action was defined by the team other than to conclude the mentioned annual report and to include the actions derived from it in the improvement plan.

b) Productions /Operations deviations
The same type of evaluation was performed for the production/operation deviations. The main conclusion was that the main cause is "Lack of Attention" with 17 deviations related with "procedure not followed" and 20 related with "operational controls/executions and decisions".
Both were related with Batch Production Records (BPRs).
This root cause has been identified prior the inspection and a Transversal Element (TE26) / Porject Charter was initiated by the Hovione Management Board members on February 2017 with the purpose of:
- Standardization of instructions (best practices) and operations throughout the areas, to use visual aids and pictures, cross checks, re-confirmation of important/critical instructions;
- Establishment of links between BPRs and area interfaces (analytics or other planning tools);
- Decrease opportunity for "filling errors" and "interpretation errors";
- Inclusion of operational instructions that may be just at high level procedure (SOPs) in the operational document.

Timeline: design phase until end of Dec.2017; implementation to occur during FY2018.

The Obs. 1a) Action Plan status

Observation #1a: Corrective action plan	**ID#**	**Status**	**Implementation Date**
1.a.1. Improvement of current Deviation Management System, specifically (but not limited to): i) Implementation and standardization of investigation methodologies. This will improve the investigation efforts and conclusions; ii) Improve definition of reoccurrence and implementation of a tool that will ease the verification of reoccurrence. This will allow improvement in identifying reoccurrence and in the root-cause analysis, solutions effectiveness evaluation and crosswise implementation; iii) Improve the CAPAs, solutions, definition (the effectiveness criteria and expected outcome must be clear the, and better understanding of the transversal potential of the CAPAs is required);	Charter 01/2017 (see Annex 1) (1)	Under implementation	Gate reviews by: 16 June 2017- **completed** 16 Oct. 2017 5.Jan 2018

iv) Implement a monitoring system (including trend analysis) to continuous evaluate the deviation system performance			

The Obs. 1a) Action Plan status (cont.)

Observation #1a: Corrective action plan	ID#	Status	Implementation Date
1.a.2. Re-evaluation of 2016 CAPAs which concluded in human error as root-cause. Identify patterns in the observation, check for reoccurrences within and cross-facility and establish a continuous improvement plan with defined actions and due dates.	CAPA #56207	**Completed**	16.Jun.2017
1.a.3. Revise the HQ.CCO.COP014 to refine definitions, provide more detail on investigation mechanisms, root cause analysis, trend evaluations and CAPA effectiveness evaluation according to the outcome of 1.a.1 activities	CAPA #56323	**Completed**	16.Jun.2017
1.a.4 Training to all staff involved in deviations and OOS (minimally but not limited to Manufacturing, QC, QA), on the updated procedure and improved methodologies namely with respect to the 30 day limit to close or justify an extension period for closure	CAPA #56350	**Under preparation with external entity**	16.Oct.2017

(1)- see letter dated 7th April 2017

OBSERVATION 1 - (Quality System) – Response #1b – Action Plan status

Hovione HQ.CCO.COP030.1.EN – Recall procedure, the Mock Recall protocol and the Recall Protocol were revised and included in our letter from 7th of April 2017.
The status of the actions defined is as follows:

- Action 1.b.6 - Execute Mock Recall (following the updated procedure) with at least one client
  The Annex 1.b.6.1 shows an example of a Mock Recall protocol completed with the information received from the customer, demonstrating that the procedure is robust and able to reconcile all the material since final packaging at Hovione up to the pharmacies.

- Action 1.b.7 - A letter was sent to all customers with whom we have a Quality Agreement signed during the last 12 months. This letter was first planned to be sent to all customers and a plan to update them was prepared. As the number of Quality Agreements is huge and some are under revision it was decided to restrict the notification to customers with whom we have signed Quality Agreements in the last 12 months (in all sites). See copy of the letter in Annex 1.b.7.1.
  Some customers have already replied stating that they are open to participate.

- Action 1.b.8 - Training to all relevant areas to ensure alignement on the application of the new protocols at all Hovione sites was provided and the action is considered completed. Evidences of the training in Annex 1.b.8.1

The Obs. 1.b). Action Plan status

Observation #1b: Corrective action plan	ID#	Status	Implementation Date
1.b.1 - Update the Mock Recall protocol to include the communication with the clients and expectations on their response	PdA # 6927	Completed	07.Apr.2017
1.b.2 - Recall protocol to be issued including the communication with the clients	PdA #6927	Completed	07.Apr.2017
1.b.3 - HQ.CCO.COP030 "Recall Procedure" to be revised accordingly	PdA #6927	Completed	07.Apr.2017
1.b.4 - Update the Hovione Quality Agreement template to include the availability for client participation on a Mock Recall with Hovione, whenever requested (see Annex 3)	CAPA #56205	Completed	07.Apr.2017
1.b.6 - Execute Mock Recall (following the updated procedure) with at least one client	CAPA# 56206	**Completed**	**12 June 2017**
1.b.7 – a letter will be sent to all customers with whom we have a Quality Agreement in place notifying them that their cooperation in a Mock Recall exercise is a requirement from FDA inspection and a plan for review of the Quality Agreement is needed	CAPA#56243	**Completed**	**09 June 2017**
1.b.8 – Training of relevant areas on changes in procedures in all sites	CAPA#56244	**Completed**	**12.Jun.2017**

OBSERVATION 2 - (Quality System) – Action Plan status

Elements described in observation #2a and 2#b are related with the deficiencies in procedure *HQ.CCO.COP014.11.EP – Deviation Records*. The Status of the action plan defined is described above in the Observation #1a and summarized in the below table.

Obs. 2a) and 2b) Action Plan status

Observation #2a and #2b: Corrective action plan	ID#	Status	Implementation Date
2.a.b.1 - Revision of HQ.CCO.COP014.11.EP procedure (the same as in the Action Plan 1.a.3.)	CAPA#56323	**Completed**	16.Jun.2017
2.a.b.2 - Training to all staff involved in deviations and OOS (minimally but not limited to Manufacturing, QC, QA), on the updated procedure and improved methodologies namely with respect to the 30 day limit to close or justify an extension period for closure.	CAPA#56350	**Under preparation with external entity**	16.October.2017

Obs. 2a) and 2b) Action Plan status (cont.)

Observation #2a and #2b: Corrective action plan	ID#	Status	Implementation Date
2.a.b.3 - Re-evaluation of past-due OOSs. Determination of criticality, and definition of immediate action in case of product quality impact. Definition of realistic extension dates (the same as in the Action Plan 1.a.2.)	CAPA #56207	**Completed**	16.Jun.2017

Elements described in Observation #2c are related with the pallet truck scale BA2001 dedicated to Building 15 operations. To prevent reoccurrence of similar situations, we have defined the appropriate criteria that will require a Preventive Maintenance Plan (PM) to be established for any equipment that meets such criteria. This required an update to the maintenance procedure (HQ.MC.IOP013.A1.1.PO).
The equipment qualification form templates in force, were evaluated and no action was identified as for new equipment is already defined in the forms the requirement to define the preventive maintenance plan.
The status of the actions defined is summarized in the following table.

Obs. 2c) Action Plan status

Observation #2c: Corrective action plan	ID#	Status	Implementation Date
2.c.1 – Inclusion of PM in SAP system for the pallet truck scale BA2001	Immediate action during inspection	Completed	16.Mar.2107
2.c.2 – Inclusion of PM in SAP system for all remaining pallet truck scales used at the site	Immediate action during inspection	Completed	16.Mar.2107
2.c.3 - Revise maintenance procedure HQ.MC.IOP013.A1.1.PO with definitions of the criteria for setting up a Preventive Maintenance Plan for any equipment (See Annex 2.c.3.1)	CAPA#56211	**Completed**	05.Jun.2017
2.c.4 - Update equipment qualification forms to include an assessment for the inclusion of PM	CAPA#56212	**Completed**	28.Apr.2017

Observation #2d related with the procedure HQ.GQ.IOP048.3.PO – "Identification and Cleaning of Utensils and Pieces of Equipment" in place at the inspected site applicable to all utensils and equipment spare parts new or in use that are, or may be in contact with the product.
During the inspection the procedure was revised to clear state its applicability to hoses. Later it was identified that additional clarifications should be included and a new revision was performed and operational areas trained on the newest version. The training initially planned to be completed by 28th of April was delayed and was completed on 18th June 2017.

As mentioned in our letter from 7th of April 2017 all Hovione sites were informed of the Form 483 and requested to assess the status in their own sites related to the same or similar situations.
The sites evaluated their own procedure and all were found in line with the cGMPs. The utensils and auxiliary equipment were checked and found in line with the site procedure. No specific improvements were identified.

This action is considered completed.

Obs 2d) Action Plan status

Observation #2d: Corrective action plan	ID#	Status	Implementation Date
2.d.1 – Correct the situation of the PT01 hoses: the hoses were dully marked as dedicated to PT01 and the ends covered with a plastic bag and labelled as "Cleaned and inspected"	Immediate action during inspection	Completed	16.Mar.2017
2.d.2 – Assess and correct if needed, labelling of the remaining hoses used at the site	Immediate action during inspection	Completed	30.Mar.2017
2.d.3 - Update procedure HQ.GQ.IOP048 to include clear guidance on the identification, cleaning, use, labelling, verifications	Immediate action during inspection	Completed	16.Mar.2017
2.d.4 – Training to all manufacturing areas on the new revised procedure HQ.GQ.IOP048 will be provided	CAPA#56327	**Completed**	18.June.2017
2.d.5 – All sites will update if need there own procedure, and will prepare an implementation plan	CAPA# 56436	**Completed**	14.Jun.2017

OBSERVATION 3 - (Laboratory System) – Action Plan status

The Obsevation #3 is related with the Liquid Nitrogen control. The Validation Mastrer Plan HQ.QSD.VMP089.0.EN includes all types of nitrogen used at the site. As per the plan the Liquid Nitrogen is the most critical system and all actions defined are now closed. Summary of the status below.

1) Introduce Nitrogen testing plan at each Point-of-Use
   Several Point-of–use were analysed as per the sampling plan defined. The analytical results obtained although with no impact on the product quality and safety due to the use of ultrafiltration in each Point-of-use, revealed the need to implement some improvements in the distribution system. An improvement plan is under preparation to be approved by the site top management in September 2017.

2) Liquid Nitrogen supplied to Hovione
   The control of the Liquid Nitrogen received was based on a certificate of conformity received together with each tank truck load supplied.
   To implement a periodic full analysis two actions were defined in February 2016 with due date of 30.May.2017, which included the approval of an outsourcing Lab for Nitrogen purity testing and associated Supplier Qualification.

A 3rd party laboratory was identified and qualified as per Hovione procedure (see Annex 3.2.1 – supplier qualification record form) and the first Liquid Nitrogen sample provided for analysis. Results will be provided to Hovione by 23rd of June. From now on the full analysis will be performed annually.

Obs. 3 Action Plan status

Observation #3: Corrective action plan	ID#	Status	Implementation Date
3.1 - Implementation of full analysis at appropriate intervals	CAPA #46353	**Completed**	30.May.2017
3.2 - To qualify an external laboratory to perform the purity testing	Change Control request #6742	**Completed**	19.May.2017

OBSERVATION 4 - (Quality System) status

This observation is related with GMP training. As described in the Hovione Letter from 7th of April the GMP refresh training to the 3 main operational areas: manufacturing, warehouse and quality control has now one year frequency at all sites. The procedure HQ.CCO.COP007-A1 was updated to include the new frequency (see Annex 4.2.1) and the new Corporate GMP training program which now includes e-learning sessions. Additionally a new Training Management System (IT) tool is now entering the validation phase. Fully implemented this will support better control of the training status across all areas and sites.

Obs. 4. Action plan status

Observation #4: Corrective action plan	ID#	Status	Implementation Date
4.1 - Implementation of an improved corporate GMP training program, that will increase the refresher GMP training frequency to at least once per year	Change Control Request #6626	**Completed**	16.Jun.2017
4.2 - Review the training procedure CCO.COP007-A1 to include the new corporate GMP training program details for the Loures Site	Change Control Request #6626	**Completed**	13.Jun.2017

OBSERVATION 5 - (Material System) completed since 7th of April 2017

Obs. 5. Action plan

Observation #5: Corrective action plan	ID#	Status	Implementation Date
5.1 – Create a segregated and locked area in the warehouse B8 raw materials storage area to place all rejected/returned/recalled raw materials and intermediates	Immediate action during inspection	Completed	16.Mar.2017
5.2 – Place the three rejected materials referred in this observation in the new area (5.1)	Immediate action during inspection	Completed	16.Mar.2017

OBSERVATION 6 - (Facility and Equipment) status

Facility and equipment repair status should be performed periodically. All sites were requested to carry out a similar assessment as the one performed at the inspected site. The information received from the sites is

summarized in the Annex 6.7.1. All sites have now defined in SAP System a periodic walkthrough activity to assess the installations status of repair. This activitiy is recorded in the SAP system.

Obs. 6. Action plan status

Observation #6: Corrective action plan	**ID#**	**Status**	**Implementation Date**
6.1 – Repair the warehouse zipper door	Immediate action during inspection	Completed	16.Mar.2017
6.2 – Seal exit door located in the north side of Building 15, fifth floor, near Reactor #RV2512	Immediate action during inspection	Completed	16.Mar.2017
6.3 – Seal exit door located in the west side of Building 15, fourth floor, near Reactor #RV4010	Immediate action during inspection	Completed	16.Mar.2017
6.4 – Check all doors from Loures Site operational areas building (production areas, warehouse, laboratories, etc.) and if possible correct as need	CAPA #56343	Completed	07.Apr.2017
6.5 - Prepare a list of all identified doors, windows and piping entrance per operational areas building (production areas, warehouse, laboratories, etc.), requiring intervention with location and status for SC site – Annex 9	CAPA #56344	Completed	07.Apr.2017
6.6 – Include in SAP PM the verification of the status of repair of doors and windows for all the site operational areas buildings (production areas, warehouse, laboratories, etc) – Annex 10	CAPA #56347	Completed	07.Apr.2017
6.7 – All sites to perform a walkthrough to identify improvements. A list with the improvements required if applicable and a correction plan to be issued.	CAPA #56438	**Completed**	14.Jun.2017
6.8 – Implementation of periodic walkthrough menchanisms to ensure continuous maintenance of sites	CAPA #56441	**Completed**	14.Jun.2017

All actions defined in our letter from April 7th with a due date prior or at the first gate review (16.Jun. 2017) were completed as planned.

We believe that the degree of accomplishement of the defined actions demonstrates Hovione commitment to comply with GMPs and to meet FDA inspectors expectations.

Attached are the evidences of the implementation of the actions considered as completed however please do not hesitate to contact us should you require any further clarification or should you wish to receive copies of other documentation to evidence compliance with commitments set out above.

CMC17.006
Food and Drug Administration

19th June 2017

We plan to perform a new gate review by 16th October 2017 where most of the pending actions will be completed with the exception of the verification/control phase of the deviation management system improvement project (see action plan1.a.1), which as mentioned will be extended up to 5th of January.

Assuring you of our best regards, we remain

Yours sincerely,

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List of enclosures:

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