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 Ave, Bldg 51, Rm 4359 Silver Springs, MD 209993 (301) 796-3334 Fax: (301) 847-8738 Att. Elizabeth Philpy or Temeka Moore,	12/01-05/2014
	FEI NUMBER 3002807208

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Nuno Duarte de Almeida, Plant General Manager

FIRM NAME	STREET ADDRESS
Hovione FarmaCiencia SA	Sete Casas 2674-506
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Loures, Portugal	Drug Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

(Facility and Equipment System)

OBSERVATION 1

Your operational qualification of the production reactors located in Building # 15 and identified as R301, R302, R801, RV 4010, R190, R230, R207B, R201, R705, R300 and R208 used for in the production of APIs, including [redacted] is inadequate in that the RPMs of the impeller shaft rotation from each reactor was never challenged at their current working range. Moreover, the mixing capabilities of them have never been verified or challenged as part of a preventive maintenance program since their initial qualification that have occurred in or around 1997 for the majority of them.

(Laboratory System)

OBSERVATION 2

Your Quality Unit Failed to establish the specificity of the test method.

Specifically,

Data supporting validation activities performed by your Quality Unit to demonstrate the suitability and adequacy of the analytical test method to be used for the release and stability testing of [redacted] Active Pharmaceutical Ingredient [redacted] was found to be inadequate in that,

a) Raw data and documents presented by your Quality Unit supporting the validations of the non-compendial Assay and Related Substances analytical test method for [redacted] API do not contain an adequate specificity degradation study due to the presence of an unknown peak (about 9.5 ~~3.5~~ minutes) that co-elute with the main peak of interest (API). Nonetheless, this validation was reviewed and approved by your Quality Unit.

RA 12/5/2014

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Jose A. Lopez Rubet, Chemist	Ramon Hernandez, Investigador Jose A Lopez Rubet, Chemist	12/5/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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Food and Drug Administration, CDER/OC/DMPQ/ICT 10903 New Hampshire Ave, Bldg 51, Rm 4359 Silver Springs, MD 209993 (301) 796-3334 Fax: (301) 847-8738 Att. Elizabeth Philpy or Temeka Moore,	12/01-05/2014 FEI NUMBER 3002807208

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Nuno Duarte de Almeida, Plant General Manager

FIRM NAME	STREET ADDRESS
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OBSERVATION 3

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,

For the deviation ID: 26014, dated 03/25/2013 and CAPA report ID: 27555 completed on 04/22/2014, your Quality Unit failed to adequately investigate, establish a root cause, or implement corrective and preventive action for the Out Of Specification (OOS) [redacted] of the assay testing for [redacted] Active Pharmaceutical Ingredient [redacted]

Inspection Dates: 12/1, 2, 3, 4 & 5, 2014

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
		Ramon Hernandez, Investigador **Jose A Lopez Rubet, Chemist**	12/05/2014

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under unsanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

Hovione

CMC14.050
Food and Drug Administration

Hovione FarmaCiencia SA
Sete Casas
2674-506 Loures
Portugal

CMC14.050

23rd December 2014

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Food and Drug Administration
10903 New Hampshire Avenue
Building 51, Room 4359
Silver Spring, MD 20993
USA

To the attention of: Mrs. Elizabeth Philpy and Mrs.Temeka Moore.

Re: FDA pre-approval Inspection carried for [redacted] *and* [redacted] carried out from 1st December to 5th December 2014

Dear Mrs. Philpy and Mrs. Moore,

We refer to the inspection to our facilities in Sete Casas, Loures – Portugal, performed by your investigators Mr Ramón Hernández and Mr. Jose Lopez from 1st December to 5th December 2014.

This letter is our response to the three observations that occurred during the inspection and were reported in the Form 483 issued.

OBSERVATION 1 - (Facility and Equipment System)
"Your operational qualification of the production reactors located in Building # 15 and identified as R301, R302, R801, RV 4010, R190, R230, R207B, R20l, R705, R300 and R208 used for in the production of APIs, is inadequate in that the RPMs of the impeller shaft rotation from each reactor was never challenged at their current working range. Moreover, the mixing capabilities of them have never been verified or challenged as part of a preventive maintenance program since their initial qualification that have occurred in or around 1997 for the majority of them."

Response:
It is Hovione practice to test agitation speed for reactors at the time of the reactor initial operational qualification and the outcome recorded in the respective qualification form.
A calibration plan for reactor agitation speed has never been in place at Hovione. Historically, for the majority of the manufacturing processes in place at Hovione the stirring speed is not defined as a critical or important process parameter.
When the stirring speed is not identified as critical nor important process parameter, the stirring speed to use in each step is defined during production by visual perception of the mixing profile inside the reactor, and it is batch size dependable. Typically, the range that is chosen allows for the observation of good mixing without splashing of the reaction mixture to the walls.
However during development, validation or at commercial stages the stirring speed is defined in specific process steps. The related Master Batch Production record and/or Process Operation Manual includes an instruction with the speed range required. This is the case of the [redacted] (Hovione internal code CH03).

Hovione recognizes the deficiency in our current procedure and the need to improve our control over the agitation speed to ensure that all manufactured batches are produced in a reproducible and consistent manner.

To address this observation the following corrective and preventive actions were identified and are being implemented:

1.1 Correction:
All the agitation speeds for the process equipment reactors used in the manufacturing process of [redacted] have been verified. During the verification process some deviations have been identified and investigated in 4 out of 10 reactors used in the [redacted] processes (refer to Annex 1.1 – Deviations summary), and none of such processes had stirring speed classified as a critical or important process parameters. The calibration records for Building 15 - [redacted] process reactors agitators can be found in Annex 1.2.
This correction has been concluded.

1.2 Corrective actions:
All agitators of the process equipment reactors used in the manufacturing process of [redacted] have been included in the SAP calibration plan (Refer to Annex 1.3 – SAP calibration plans for Building 15 - CH03 process reactors agitators).
This corrective action has been concluded.

1.3 Preventive actions:

1.3.1 All the agitators of process equipment (reactors and other equipment) will be assessed (Event ID 37099 opened in Hovione CAPA System) and will be included in the site SAP calibration plan according to the following time schedule:
Actions:
a) Reactors: to be concluded by 31.March.2015;
b) Other equipments as applicable: to be concluded by 30.June.2015.

1.3.2 Update the Hovione qualification procedure to clearly state that the verification of the agitation speed should be included in the Calibration Program for its periodic full scale verification. The frequency of the verification will depend on the type of equipment and intended use. We will also consider this matter in technology transfers. DQ.SOP140 - Systems Qualification – will be updated by 31.Mar.2015.

OBSERVATION 2 - (Laboratory System)
"Your Quality Unit Failed to establish the specificity of the test method.

Specifically,

Data supporting validation activities performed by your Quality Unit to demonstrate the suitability and adequacy of the analytical test method to be used for the release and stability testing of [redacted] was found to be inadequate in that,

a) Raw data and documents presented by your Quality Unit supporting the validations of the non-compendial Assay and Related Substances analytical test method for [redacted] API do not contain an adequate specificity degradation study due to the presence of an unknown peak (about 10.5 minutes) that co-elute with the main peak of interest (API). Nonetheless, this validation was reviewed and approved by your Quality Unit."

Response:
With regards to [redacted] (Hovione internal code TR68).
We acknowledge that the peak with the retention time of about 10.5 (RRT1.08) that co-elutes with the main peak of interest (API) was not evaluated during the study and that no justification was included in the validation report (HQ.QSR.MV813.0.EN – CRLC4265-17TR68 and 17TR68M: Identification and Related Substances (by HPLC) – Method Validation Report) (Refer to Annex 2.2.).

This decision was taken because this impurity is neither an unknown impurity nor a degradant. The identity of this peak was identified as a process-related impurity by the previous manufacturer. The origin of this impurity is understood and well-controlled in the current manufacturing process and is not present in the final API at reportable levels (level of detection of <0.04% area). As such, this peak is not a specified impurity and so was not required to be evaluated as part of the selectivity criteria for validation. Hence, the Quality Unit approved the analytical method validation report (HQ.QSR. MV813.0.EN – CRLC4265-17TR68 and 17TR68M: Identification and Related Substances (by HPLC) – Method Validation Report) (Refer to Annex 2.2) in accordance with ICH, Q2(R1), and determined to be suitable for its intended purposes of batch release and stability testing.

More detailed information for not having included the peak in the study and commitment to method re-validation are now presented in Annex 2.1.

Notwithstanding the above mentioned and based on the discussions we had have during the inspection we decided to repeat the validation of the analytical method according to the protocol HQ.QSP.MV839.0.EN (Refer to Annex 2.3.).
The proposed protocol includes additional information gathered after the first validation of the method namely in what refers to:

i) Forced degradation conditions to enhance degradation effectiveness (Refer to Annex 2.4.);
ii) Evaluation of the performance of the two types of columns to clearly demonstrate their interchangeability. The columns used are both from the same supplier with the same part number and the same stationary phase packing material however with a different model code (QT and WT). According to the supplier these columns differ with regard to the column endfitting. The WT designates a column having a threaded column endfitting while the QT designates a column having a quick seal endfitting. Both type of columns were used in the original method validation study and are being used in the release and stability analysis.
iii) Definition of a robust system suitability criterion to ensure selectivity of the endogenous impurity (RRT 1.08).

Actions:
2.1 The analytical method validation protocol now proposed will be executed until 06.Mar.2015;
2.2 The report will be finished by 03.Apr.2015 as per the following schedule:

a) Starting date: 26.Jan.2015
b) Forced degradation work: 16.Feb.2015
c) Full validation work completed: 06.Mar.2015
d) Report approved: 03.Apr.2015

A copy of the report will be sent to your attention for your review.

OBSERVATION 3 - (Laboratory System)
"There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,

Hovione

CMC14.050
Food and Drug Administration

For the deviation ID: 26014, dated 03/25/2013 and CAPA report ID: 27555 completed on 04/22/2014, your Quality Unit failed to adequately investigate, establish a root cause, or implement corrective and preventive action for the Out Of Specification (OOS) (stability batch TE-17TR68M.HQ00002-06M-T25H60&T40H75 and TE-17TR68M.HQ00003-06M- T25H60) of the assay testing for [redacted]

Response:
With regards to [redacted] (Hovione internal code TR68)
The OOS result investigation that was performed pointed out clearly that the root cause for the OOS results was an "unclear procedure" in the solution preparation. This conclusion was achieved based on a thorough review and assessment of the event which was considered by the quality unit as correct. The actions defined were implemented and considered appropriate, since that time no other similar occurrences have been recorded.

A detailed description of the investigation is presented in Annex 3.1.

Notwithstanding the above mentioned and from the discussions that occurred during the inspection we acknowledge that the investigation performed could have been better described.
While other potential root causes that were raised have been ruled out, our experience suggests that there is still an opportunity to improve sample preparation procedures. To address this, a deeper evaluation was performed by a wider team and a protocol was issued to evaluate the dissolution procedure in place for TR68 product. Please see protocol HQ.QSP.FT042.0.EN in Annex 3.2. The ultimate objective of this study is to improve the sample preparation procedure to ensure better consistency in the method results.

Actions:
3.1 The Protocol will be executed until the 23.January.2015;
3.2 The conclusions drawn will be incorporated in the method and applied to the validation work (referred in Observation 2) that will start afterwards - target date: 26.Jan.2015;
3.3 For the future, a default procedure for product dissolution will be implemented based on the outcome of the above proposed study – target date: 03.Apr.2015.

We trust this response addresses adequately the three 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 the other documentation mentioned or of evidence of compliance with commitments set out above.

We plan to have all actions set out above completed by 31.Jul.2015 as per the Action Plan in page 6.

Assuring you of our best regards, we remain
Yours sincerely,

Guy Villax
Chief Executive Officer
Tel: +351 21 982 9381
Cell: +351 917 888 899
gvillax@hovione.com

List of enclosures:

Annex ref:	Description	Cover letter page	Separated folder
Annex A	Action Plan revision 0	6	
Observation 1			
Annex 1.1	CH03 speed rotation deviations summary	7-8	
Annex 1.2	Calibration records for Building 15 - CH03 process reactors agitators		√
Annex 1.3	SAP calibration plans for Building 15 – CH03 process reactors		√
Observation 2			
Annex 2.1	Rationale for the non-inclusion of the impurity with RRT1.08 in the selectivity testing	9	
Annex 2.1.1	Manufacturing Process Control on the RRT 1.08 impurity in [redacted] Drug Substance [redacted]		√
Annex 2.1.2	HQ.CR.LC4265.4.EN – 17TR68 AND 17TR68m: Identification, Assay and Related Substances determination (by HPLC)		√
Annex 2.1.3	GQSP3526 – 17TR68M Specification		√
Annex 2.1.4	NJ.CR.LC4509.1.EN – TR68: 16TR68020 Identification, Purity, Related Substances and Assay (by HPLC)		√
Annex 2.2	HQ.QSR.MV813.0.EN – CRLC4265-17TR68 and 17TR68M: Identification and Related Substances (by HPLC) – Method Validation Report		√
Annex 2.3	HQ.QSP.MV839.0.EN - CRLC4265-17TR68 and 17TR68M: Identification and Related Substances (by HPLC) – Method Validation Protocol		√
Annex 2.4	Forced degradation conditions to enhance degradation effectiveness report		√
Observation 3			
Annex 3.1	Description of the OOS investigation	10-14	
Annex 3.2	Sample preparation optimization studies protocol – HQ.QSP.FT042.0.EN		√

CC: Ramon Hernandez - Investigator
Jose Lopez – Chemist
Sponsors: appropriately redacted.

Annex A- Hovione Loures site - FDA Inspection Dec.2014

Action plan and status report to adress the Form 483 dated 5Dec2015 - version 00 22Dec2015

Your Obs. No.	Our Audit Finding No.	Inspection Finding Description	Action No.	Corrective / preventive action description	Our CAPA No.	Target date for completion	Status	Completed on:
1	37099	Reactors impeller shaft rotation not challenged as part of the preventive maintenance program since their initial qualification	1.3.1.a	All the agitators related with reactors will be assessed and included in the site SAP calibration plan	37361	31-Mar-2015	ongoing	
			1.3.1.b	All the agitators from other process equipment will be assessed and included in the site SAP calibration plan	37362	30-Jun-2015	ongoing	
			1.3.2	Update of Hovione internal procedure DQ.SOP140	37363	31-Mar-2015	ongoing	
2	37100	Raw data and documents presented by your Quality Unit supporting the validations of the non- compendial Assay and Related Substances analytical test method do not contain an adequate specificity degradation study due to the presence of an unknown peak that co-elute with the main peak of interest (API)	2.1	Re-validation of the analytical method HQ.CR.LC4265 - protocol execution	37100	6-Mar-2015	Not yet started	
			2.2	Analytical method validation report approval		03.Apr.2015	Not yet started	
3	37101	There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed	3.1	Evaluation of the dissolution sample procedure as per the defined protocol	37364	23-Jan-2015	Not yet started	
			3.2	Revision of the analytical method	37365	26-Jan-2015	Not yet started	
			3.3	Evaluation of the dissolution sample procedure as per the defined protocol	37366	03.Apr.2015	Not yet started	

ANNEX 1.1

Hovione Form 483

Inspection to Loures site - 1 to 5 December 2014
Observation 1 – Facility and Equipment system

Speed rotation calibration - Summary of the investigations performed

Deviation ID	Reactor	Calibration Variation (RPM)	Root cause	Impact analysis
37033	R201	Between 8 and 40 RPM in all range	In 2007, the agitator was replaced by a new one with a different rotation speed upper limit (speed range up to 95 RPM instead of 53 RPM). Because the rotation speed was not subject to calibration, the agitator replacement didn't lead to a rotation confirmation.	Rotation speed difference after agitator replacement (after 2007 and until December 2014) Range: 10 | 21 | 32 | 42 | 53 Real: 18 | 37 | 56 | 74 | 93 The agitator replacement of R201 with the change in the stirring range could only impact in processes that were manufactured before and after the change that was performed in 2007. In this case, only one product, have been produced before and after the replacement. As it had no stirring speed defined in the BPR, nor we have ever detected any quality issues related with stirring speed, we consider that the agitation speed change had no impact on the quality of this product. In the other products that were manufactured in this reactor after the replacement of the agitator, like CH03 products, the rotation speed will be corrected in the BPR and/or in the Product Operation Manual. Nevertheless, the rotation speed will continue to be the same used in previous batches and only the registers in the BPR will now reflect the real rotation speed (corrected by a factor of 1.8 given by 95/53). Correction done now: Range: 18 | 37 | 57 | 76 | 95 Real: 18 | 37 | 57 | 76 | 95

Deviation ID	Reactor	Calibration Variation (RPM)	Root cause	Impact analysis
				Calibration was performed after the range correction meeting the MAE (Maximum Admissible Error). Specific CAPAS were created to correct this deviation and update the Manuals and BPRs.
37034	R230	-7 at 190 RPM (maximum value of the agitation range)	Incorrect configuration on maximum rotation speed on the automation system (the maximum speed at the end of the range defined in the automation system was 190 RPM and did not match the agitator motor and gear box specification of 198 RPM)	In the R230, the stirring speed is specified for consistency purposes in some steps in the BPR or manuals of some products but none of them use the maximum value (190 rpm). As the calibration variations observed in the operational range were inside the MAE, no changes are required in the BPR or Operation Manuals. The worst case observed was 7 RPM difference at the highest range of the stirring (between 158 RPM and 198 RPM). In the highest stirring ranges of the equipment, a difference of 7 RPM (2 RPM, if we consider the difference to the MAE) has no impact on the reproducibility of the process since at higher stirring speed the importance of small differences in RPM is negligible. Therefore, there is no impact on process documentation instructions.
37035	R300	-4 at 125 RPM (maximum value of the agitation range)	The root cause for the deviation at the end of the range (125 RPM) was that the motor of the agitator was not reaching its maximum speed (motor drive required adjustment)	In the R300, the stirring is defined for consistency purposes, in some steps on the BPRs of the some products varying the speed range between 30 and 50 or 100 and 110 rpm and the calibration variations were inside the MAE, thus no changes are required in the BPR or Operation Manual. For 17CH03SD, we have at the most 1 RPM difference at 110 RPM (the range where it was identified that the calibration variation was outside the MAE, was in the highest range of the stirring (between 100 RPM and 125 RPM). In the highest stirring ranges of the equipment, a difference of 4 RPM (1 RPM, if we consider the difference to the MAE) has no impact on the reproducibility of the process since at higher stirring speeds the importance of small differences in RPM is negligible. Therefore, there is no impact on process documentation instructions.
37038	R705	+6 at 199 RPM (maximum value of the agitation range)	The root cause for the deviation at the end of the range (205 RPM) was that the motor of the agitator was not reaching its maximum speed (motor drive required adjustment)	The range where it was identified that the calibration variation was outside the MAE, was in the highest range of the stirring (between163 RPM and 205 RPM). In the highest stirring ranges of the equipment, a difference of 6 RPM (1 RPM, if we consider the difference to the MAE) has no impact on the process. At higher stirring speeds, the importance of small differences in RPM is negligible. Therefore, there is no impact on process documentation instructions.

ANNEX 2.1

Hovione Form 483
Inspection to Loures site1 to 5 December 2014
Observation 2 – Laboratory System

[redacted] product is manufactured at Hovione under contract manufacturing and according with our customer [redacted] this impurity is a process impurity that is formed in the 1st (first) chemical step.
This impurity is neither an unknown impurity nor a degradant. The identity of this peak was identified as a process-related impurity by the previous manufacturer. The origin of this impurity is understood and well-controlled in the current manufacturing process and is not present in the final API at reportable levels (level of detection of <0.04%). As such, this peak is not a specified impurity and so was not required to be evaluated as part of the selectivity criteria for validation. Hence, the Quality Unit approved the validation (HQ.QSR.MV MV813.0.EN – CRLC4265-17TR68 and 17TR68M: Identification and Related Substances (by HPLC) – Method Validation Report) (Refer to Annex 2.1) in accordance with ICH, Q2(R1), and determined to be suitable for its intended purposes of batch release and stability testing. Background information and commitment to method re-validation are provided below.

The peak with an impurity exhibiting a retention time of about 10.5 minutes (RRT1.08) that co-elutes on the descending tail of the main peak of interest (API) was identified during development by the [redacted] (Refer to Annex 2.2.1). According to the Sponsor this impurity is a process impurity, not a degradant, that forms in the first GMP chemical step in the production of the [redacted] (16TR68020) intermediate. The formation of this impurity is also supported by publications in the scientific literature [redacted] It was studied by the Sponsor and later confirmed by Hovione that [redacted] manufacturing process became more robust in controlling this impurity below the detection threshold limit (<0.04% area) [redacted]. This impurity exhibits a relative retention time (RRT) of 1.04 in the analytical method used to analyse the [redacted] intermediate (Analytical method – NJ.CR.LC4509.1.EN (Refer to Annex 2.2.4). The reduction of this impurity in [redacted] is confirmed by the data for fourteen batches of this intermediate produced where four were manufactured by Hovione Technology Transfer Center in New Jersey ([redacted] as per the Table 1 in the Sponsor report, [redacted] Annex 2.2.1). One can also conclude from the data presented in Table 1 that this impurity is purged (columns 4 and 6 of the table) in the downstream process.

Only one API batch contained the impurity at a level at 0.05% while all remaining batches were below the reporting threshold (0.04%).The only batch of drug substance that contained a reportable level of the impurity was manufactured from a [redacted] intermediate that itself was prepared using [redacted] used in the current process. Therefore, the final API specifications (Ref: GQSP3526) (Refer to Annex 2.2.3) do not include limits for RRT 1.08 as a specified impurity. As such, it would not be necessary to take this impurity at RRT 1.08 into account in the selectivity study or in the degradation study as it is not a degradation product.

[1] [redacted]

ANNEX 3.1

Hovione Form 483
Inspection to Loures site 1 to 5 December 2014
Observation 3 – Laboratory System

Summary of the investigation performed on the deviation #26014

DESCRIPTION OF THE DEVIATION

During a stability study analysis at the 6 months time point for batches 17TR68M.HQ00002 and 17TR68M.HQ00003 out of specification results were obtained as presented in the following table.

Batches	Sample 1 %(w/w)	Sample 2 %(w/w)	Specification limit %(w/w)
17TR68M.HQ00002 T25H60 06M	***103.0***	101.4	≥97.0 and ≤ 102.0
17TR68M.HQ00002 T40H75 06M	101.5	**102.1**	
17TR68M.HQ00003 T25H60 06M	***102.1***	***102.1***	
17TR68M.HQ00003 T40H75 06M	101.7	101.9	

Table 1: Assay results

Assay values above 102.0% were observed in three stability samples (Out of specification) against a specification of "Not less than 97.0% w/w and not more than 102.0% w/w (anhydrous and ethanol free basis). These OOS results immediately triggered an investigation as per internal Hovione procedure COP015. This procedure requires the event to be documented on the form QSD.RF181 which was completed by the analyst and the reviewer at different steps of the investigation and annexed to the analytical package and to the deviation (#26014).

INITIAL INVESTIGATION/CONFIRMATION OF THE OOS

Laboratory Investigation

Analyst Evaluation

- Evaluation of all steps of the method by the analyst concluded that no deviations occurred.

Supervision Review

- Confirmed that the analyst did not deviate from the written analytical method, CRLC4265 (Refer to Annex 2.2.2),
  - Chromatographic profile was comparable to the reference profile
  - Visual inspection of the sample solutions showed no concerns,
  - System suitability met the acceptance criteria
  - Calculations were performed correctly.
- Confirmed all equipment used were within their respective calibration period and set up properly.

Confirmation of the OOS

Re-injection of the solution from the original chromatography vials and preparation of fresh vials containing the original working solution

- The results obtained for the same vial confirmed the result OOS, but the injection of the sample solutions in new vials showed a decrease in the assay content in relation to the initial result and in relation to the initial vial and lead to results within specification. These results are presented in the table below.

Batches	Initial		Investigation			
	SAM1 %(w/w)	SAM2 %(w/w)	SAM 1 %(w/w) Re-injection (a)	SAM 2 %(w/w) Re-injection (a)	SAM 1 %(w/w) New vial (b)	SAM 2 %(w/w) New vial (b)
17TR68M.HQ00002 T25H60 06M	***103.0***	101.4	102.8	N/AP	100.2	N/AP
17TR68M.HQ00002 T40H75 06M	101.5	**102.1**	N/AP	102.5	N/AP	101.6
17TR68M.HQ00003 T25H60 06M	***102.1***	***102.1***	102.6	102.9	101.3	101.5
17TR68M.HQ00003 T40H75 06M	101.7	101.9	N/AP	N/AP	N/AP	N/AP

Table 2 – Investigation retest results

(a) Re-injection: corresponds to performing a new injection from the same vial that was used to generate the corresponding initial result
(b) New vial: corresponds to performing a new injection from the same solution that was used to generate the initial result but maintained in the volumetric flask and taken to vial in the course of the investigation step
N/AP – Not applicable under the scope of the investigation performed

Retest the sample as per procedure HQ.QSD.RF181
Retest protocol: Three (3) analyses of the product (6 different sample weighings).
The retests were run as per the analytical method. The first re-test analysis was conducted by the same analyst using the same standard preparation. New samples were taken from the original package (stability sample). The second and third analyses were run by a different analyst with a completely new set up of the equipment (including a different column). The results obtained are presented in the table below. The retest results failed to confirm the OOS. Since the OOS could not be confirmed, the OOS is not related to product quality but to a laboratory error (most probably related to the sample preparation) that could not be unequivocally identified.

Following internal procedure HQ.CCO.COP015 the average result of the 3 retests (corresponding to 6 independent sample preparations for each batch) was used for the release of the assay result and the original results were disregarded as they did not reflect the real value of assay of the batches.

Batch	%(w/w)											
	Initial		Investigation				Re-test					
			Re-injection (a)		New vial (b)		1 (c)		2 (c,d)		3 (c,d)	
	Sample		Sample		Sample		Sample		Sample		Sample	
	1	2	1	2	1	2	1(f)	2	1	2	1	2
17TR68M. HQ00002 T25H60 6M	***103.0***	101.4	102.8	N/AP	100.2	N/AP	100.8	100.0	99.9	100.3	99.9	100.2
							Average: 100.6		RSD:0.3%			
17TR68M. HQ00002 T40H75 6M	101.5	**102.1**	N/AP	102.5	N/AP	101.6	101.3	101.7	100.8	99.9	100.5	99.5
							Average: 100.7		RSD:0.8%			
17TR68M. HQ00003 T25H60 6M	***102.1***	***102.1***	102.6	102.9	101.3	101.5	101.2	100.9	100.6	100.1	100.8	100.4
							Average: 100.2		RSD:0.4%			
17TR68M. HQ00003(e)T40 H75 6M	101.7	101.9	N/AP	N/AP	N/AP	N/AP	100.3	100.0	99.8	100.1	100.5	100.7
							Average: 100.2		RSD:0.3%			

Table 3: Retest results

(a) Re-injection: corresponds to performing a new injection from the same vial that was used to generate the corresponding initial result
(b) New vial: corresponds to performing a new injection from the same solution that was used to generate the initial result but maintained in the volumetric flask and taken to vial in the course of the investigation step
(c) New standard was prepared for system suitability purposes
(d) New standard was prepared for system suitability purposes. Different column and analyst.
(e) Batch used for control purposes (This sample was also analyzed in the same run where the OOS results were obtained but was not found OOS).
(f) During this test a result of 106% was obtained for this sample which was not considered because it was identified as a d-check failure between samples (ratio of response factors between the 2 sample preparations was found above 2%). This situation was also discussed during the inspection and as a consequence Hovione will revise the internal procedure to ensure that any sample result found outside the specification limit will be investigated as per the OOS procedure in place.
N/AP – Not applicable under the scope of the investigation performed

ROOT CAUSE HYPOTHESES

A preliminary assessment of the investigation indicated an analytical problem related to the solution in the initial vial used. Several hypotheses were proposed:

A. Contamination of the vial by a compound that co-elutes with the main peak;
B. Co-elution of a degradation impurity with the main peak;
C. Solubility equilibrium not reached inside the volumetric flask before transferring into the vial.

Evaluation of the Hypotheses

Hypothesis A – Contamination of the vial
As the vials used were new, hypothesis A was not considered further.

Hypothesis B – Co-elution of a degradation impurity with the main peak
Based on the degradation studies that were performed as part of the validation of the test procedure wherein no potential degradation product was determined to co-elute with the main peak, this hypothesis was not considered further.

Hypothesis C – Solubility equilibrium not reached in the volumetric flask before transferring into the vial

[redacted] is used to initially dissolve the drug substance sample as its solubility in that solvent is greater than 250 mg/ml. The [redacted] solution is then diluted to the analytical volume with a diluent composed of [redacted] It is perhaps possible that the use of 2 ml of [redacted] ensure the initial dissolution of the sample may create a concentration gradient inside the volumetric flask that needs time to ensure solution homogenization.

In order to investigate hypothesis C, a CAPA was issued (CAPA 27555). This CAPA described a study wherein a sample would be prepared as per the method and then left to equilibrate for 5, 10, 20 and 30 minutes before transferring the sample solution to the vials. The goal was to evaluate any potential difference in the assay results over the equilibration time span specified. .

The task defined in CAPA 27555 for evaluation of the solution stabilization time was conducted using a sample from the 9 months stability time point. All results obtained after equilibrating the sample solution for 5, 10, 20 and 30 minutes before transferring the sample solution into the vials were within the method acceptable variation (%RSD=1.2%, acceptable method variability %RSD=< 2.0%) and within the assay specification. These results are presented in the table below.

Equilibration time in volumetric flask before preparation of the vial	5 minutes	10 minutes	20 minutes	30 minutes
17TR68M.HQ00002 T25H60 09M	98.1%(w/w)	100.6%(w/w)	100.2%(w/w)	98.5%(w/w)

Table 4: Solution equilibration time test

ASSIGNMENT OF ROOT CAUSE

Although the results associated with the CAPA 27555 were inconclusive the probable root cause was assigned as "unclear procedure" for sample preparation. This assignment of root cause suggested that the method was not sufficiently detailed and lead to situations where the product could be transferred to a vial before total dissolution was reached. If the process is not carried out with clearly defined steps to ensure proper miscibility between the methanol phase (2% with 50 mg of product dissolved) and [redacted] phase the concentration gradient created during the mixing process may lead to results as the ones reported in the OOS. As a corrective action, the method was revised

to add the guidance to invert the flask several times and to allow the solution to equilibrate before transferring to vials in order to avoid this situation in the future. No other OOS was detected in the analysis of the stored stability samples which indicates that no systematic laboratory error is present. The results for the subsequent stability storage intervals are summarized in the table below.

Batch	Assay in %(w/w)									
	Storage Time (months)									
	initial	1	2	3	6	9	12	18	24	Average
17TR68M.HQ00001 T25H60	98.8	N/AV	N/AV	97.6	98.2	99.7	100.6	99.6	100.2	99.2
17TR68M.HQ00001 T40H75		99.1	100.3	98.0	100.6	N/AV	N/AV	N/AV	N/AV	99.4
17TR68M.HQ00002 T25H60	98.2	N/AV	N/AV	99.8	100.2	100.5	99.0	98.8	99.8	99.5
\17TR68M.HQ00002 T40H75		100.0	100.8	99.7	100.6	N/AV	N/AV	N/AV	N/AV	99.9
17TR68M.HQ00003 T25H60	98.8	N/AV	N/AV	99.8	100.6	100.9	100.1	98.2	99.0	99.6
17TR68M.HQ00003 T40H75		100.1	100.9	99.8	100.2	N/AV	N/AV	N/AV	N/AV	100.0

Table 5: Stability assay values

N/AV – Results not available as time point testing not required as per the stability protocol in force

FUTURE SAMPLE PREPARATION EVALUATIONS

All of the procedures in place associated with OOS and CAPA were followed to thoroughly review and explain the stability study OOS. Taking into the results of the investigations as summarized above, it was considered that the root cause defined for the deviation was correctly attributed. This OOS has not been repeated and indicates no systematic laboratory error is present.

However to confirm the robustness of the sample preparation, an evaluation of the dissolution procedure in place for TR68 product will be conducted and a protocol issued to assess the variables identified that may impact the result of the analysis (Refer to Annex 3.2). When the sample preparation procedure is found to be robust it will be incorporated into the method.

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

Division of Quality Surveillance Assessment
Inspection Assessment Branch
10903 New Hampshire Avenue
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June 9, 2015

Guy Villax
Chief Executive
Hovine FarmaCiencia SA
Sete Casas
2674-506 Loures
Portugal

Reference FEI 3002807208
Reference inspection date (s): December 1 to 5, 2014
Establishment Locale: Loures, Portugal

Dear Mr. Villax:

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,

Merideth Rose
Consumer Safety Officer
Inspection Assessment Branch

Enclosure: EIR

TABLE OF CONTENTS

SUMMARY

This Pre-approval and cGMP Inspection was conducted utilizing Compliance Program, 7346.832 Pre-approval inspections for [redacted] API [redacted], [redacted] API ([redacted] and 7356.002F, Active Pharmaceutical Ingredients Inspections. In addition, a request from CDER while we were conducting the inspection was received to collect additional information from [redacted] API under [redacted]. Hovione FarmaCiencia SA is listed as an API contract manufacturing site. This information was also verified by Mrs. Paulo, Compliance Director at the firm.

This inspection was covered under FACTS Assignment ID: 8886736. Profile Classes CSN non sterile bulk by chemical synthesis. The site only manufactures the API for these NDAs.

Hovione FarmaCiencia SA is a manufacturer of both medical devices and drugs.

The previous FDA drug inspection was conducted from 9/23-27/13 and classified as NAI, therefore no FDA 483 form was issued. Hovione is considered as a manufacturer of a component of a medical device.

The current inspection evaluated the Quality, Production, Equipment and Facility and Laboratory Controls Systems. Limited areas of inspectional coverage included Packaging and Labeling Systems. Three objectionable conditions were listed in the FDA-483 that was issued to Mr. Nuno Duarte Almeida, Plant Manager, at the end of the inspection, during a closing inspection meeting with Management. They were; inadequate operational qualification of the production reactors, failure to establish the specificity of test methods and failure to thoroughly review any unexplained discrepancies.

Mr. Duarte acknowledged the observations listed in the FDA-483 form and promised corrections and a written response within 15 working days.

Mr. Jose Lopez Rubet, Chemist from SJN-DO, participated in this inspection. Mr. Lopez was responsible for the evaluation of the Laboratory Control System. I, Ramon Hernandez, Investigator, was the team leader and wrote all other sections of this report. The laboratory section of this report was written by Mr. Lopez and is identified as JLR as well as the exhibits collected by him.

Also Mr. Pedro Marques da Silva and Mrs. Margarida Machado, inspectors, from "infarmed" (Portugal Medical Regulatory Authorities) participated during the inspection as listeners.

There were no refusals and no samples were collected.

ADMINISTRATIVE DATA

Inspected firm:	Hovione FarmaCiencia SA
Location:	Sete Casas 2674-506 Loures, Portugal
Phone:	351 21 982 9381
FAX:	351 21 982 9498

Mailing address:	Sete Casas 2674-506 Loures, Portugal
Dates of inspection:	12/01/2014, 12/02/2014, 12/03/2014, 12/04/2014, 12/05/2014
Days in the facility:	5
Participants:	Ramon Hernandez, Investigator Jose A. Lopez Rubet, Chemist

On 12/01/104 credentials were presented to Mr. Nuno Duarte de Almeida, Site Manager who introduced himself as the most responsible person on-site at the time of this inspection. Mr. de Almeida explained that Mr. Guy Villax, CEO was out of town on a business trip for the week. But that he will be present during the inspection close out meeting. On 12/02/2015 Mr. Pedro Marques da Silva and Mrs. Margarida Machado, inspectors, from "infarmed" (Portugal Medical Regulatory Authorities) joined us during the inspection as listeners.

FDA correspondence should be addressed to:

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Or
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HISTORY

Hovione FarmaCiencia SA is part of Hovione Holding Limited. The company was founded by Ivan Villax, Ph.D. in 1959 and the first plant was built in Loures, Portugal in 1969. The company has manufactured commercial active pharmaceutical ingredients. The Loures, Portugal location has been inspected by FDA several times, with the first inspection being conducted in 1982. In addition, in 2011 the FDA conducted a QBD inspection.

Hovione has four business units to include Exclusives (i.e.: R&D, process validation, PAR studies, clinical API supply), Inhalation (i.e.: formulation/device development, powder characterization, morphology analysis), Particle Design (i.e.: spray drying, freeze drying, micronization, and milling) and Generics (i.e.: APIs, tetracyclines and corticosteroids) with a production volume of 430 metric tons. Total sales in 2013 were $202 million USD.

Hovione FarmaCiencia SA, Loures Portugal site is considered the Headquarter site and encompasses approximately 37,300 square meters. The plant consists of 15 multi-purpose buildings/blocks. **Exhibit RH #1** shows copy of the facility layout

In addition, Hovione has multiple locations globally to include sites in China (Macau), Ireland (Cork), and the U.S.(New Jersey). Hovione ships drug products globally to main markets in North America, Europe, Japan, Australia and New Zealand.

The firm operates 24 hours a day, 7 days a week in two or three shifts with four teams. There are approximately 639 employees on-site to include: 40% Production, 10% R&D, 12% Administration, 6% QA/Compliance, 5% Engineering and Utilities and 19% QC Lab & Analytical Chemistry.

The firm is registered with FDA under FEI # 30002807208. **Exhibit RH# 2** shows copy of the firm registration and drug product listing.

Changes since last inspection conducted on September 2013 includes;

- Stability samples storage was outsourced to 3S Bluestabil
- Introduction of 2 new commercial products:
  - Doxycycline Hyclate (MA51)
  - Doxycycline Monohydrate (MA64)
- Spray dryer [redacted] facility was upgraded to produce intermediate drug product
- Micronizer [redacted] was transferred from Building 15 to B13

INTERSTATE COMMERCE

Hovione FarmaCiencia SA manufactures and distributes the following APIs to the U.S.:

- Hydrocortisone Aceponate Micronized [redacted].
- Doxycycline Hyclate [redacted]
- Mometasone Furoate [redacted]
- [redacted] API and Spray Dried Dispersion [redacted] for [redacted]

Among others, these APIs are directly shipped to [redacted].

Mrs. Paulo provided a list of all products manufactured at the site and shipped to the continental USA since 2012 **(Exhibit RH #3)**.

JURISDICTION

Mrs. Paulo provided a list of U.S marketed products shipped to the United States to include the material name, batch #, quantity, customer and address shipped to, and delivery date **(Exhibit RH #3)**.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Key Management at this site includes:

- Guy Villax, CEO – is the son of the company founder and is the most responsible person on-site.
- Nuno Duarte de Almelda - Site Manager has been in this position for 6 years.

- Luisa Paulo - Compliance Director has been with the company for 30 years.
- José Lisboa – Quality Assurance Director has been with the company for 30 years.
- Joana Ferreira – Head of Quality Systems Management has been with the company for 16 years.
- Joana Mateus – Head of QA Drug Products, Technical Operations has been with the company for 14 years.
- Luis Gomes, Vice-President- Manufacturing

Other personnel who provided information during this inspection include the following:

- Irina Rodrigues–QA Technical Expert
- Maria Carlos–QA Technical Expert
- Elisabete Duque–QA Technical Expert
- Mario Rodrigues–Engineer Pilot Plant
- Alexandra Silva–Director of Analytical Chemistry
- Miguel Cansado–Senior Project Manager
- Luis Segadaes–Head, Production B7
- Elisabete Mateus–Senior Chemist RD PCD
  Alvaro Lopes–Head, Production Exclusives B15
- Manuel Carvalho–Head of Warehouse
- Jose Manuel–Warehouse Supervisor
- Rui Duarte–Warehouse Operator
- Leandro Martins–Analytical Instrumentation Technician
- Nuno Rebelo–QA Technical Expert
- Vera Fernandes–Analytical Chemist-Stability
- Ricardo Gariso–Assistant Technical Expert-Chromatography
- Rui Tempero Qualification Technical Expert-Engineering
- Sergio Guerreiro–Qualification Technical Expert-Engineering
- Patricia Bernardino–Maintenance Engineer
- Teresa Barao–Head of Qualification and Validation
- David Martins–Production Director
- Ilda Chasqueria–Technical Expert-MF Operational Support
- Jose Carlos Santos–Production Operator
- Manuel Carvalho–Warehouse and Water System Manager

Mrs. Paulo explained there have been no major changes to management since the previous FDA inspection. In addition, Mrs. Ferreira provided a copy of the organizational charts of Hovione FarmaCiencia SA to include the Hovione Group, QA Development, QA Technical Operations, and Production Area as **Exhibit RH # 4**

FIRM'S TRAINING PROGRAM

The firm has a training program and continues to update employees on-the-job in specific areas where they work on a yearly basis and general GMP aspects. SOP No. HQ.CCO-COP.007.4.EP, Version 4 Effective date: 3/15/13 "Training" was on site for employee training. I reviewed training evidence from employees and I did not observe any objectionable condition.

GMP training involves different departments that are issued different modules dependent on responsibilities. There are classroom, practical workshops, and e-learning modules. The Compliance Department is involved in developing the GMP training, and is responsible for the training that is performed. HR will monitor the training.

MANUFACTURING/DESIGN OPERATIONS

[redacted] API listed in [redacted] (product code 17[redacted])

The synthesis of [redacted] involves five steps. There are four proposed regulatory starting materials in the manufacture of the drug substance. The same synthetic route has been used throughout clinical development with minor modifications. For non-clinical, Phase I and Phase II study supplies; the drug substance was isolated [redacted] from aqueous solution. For Phase III and commercial production a spray drying process was developed that allows production of larger batches up to [redacted] These batches obtained by spray drying process have been used for later stage nonclinical studies as well as for the production of the registration batches and the same route will be used for commercial production once the application is approved.

Production process including equipment train for the manufacture of [redacted] API is included as **Exhibit RH# 5.**

[redacted] API listed in [redacted] (product code [redacted])

[redacted] is a [redacted] being developed for the prevention [redacted] is being developed in oral and intravenous formulations.

Hovione FarmaCiencia Loures facility will be responsible to perform only the micronization process to [redacted] API. [redacted] API is received at Hovione Loures facility from Hovione New Jersey site and fully tested prior to be released for further micronization step. Once the product is micronized, is fully tested again including particle size test and then released.

[redacted]

During current inspection we were requested by CDER to collect additional information related to [redacted] API [redacted], [redacted] was approved in January 2012 by the FDA, as notified by [redacted] the NDA holder. This product application was reviewed during FDA last Inspection (September 2013).

The drug intermediates, API and drug dispersion of the API are conducted at Hovione FarmaCiencia SA. The intended use of the finished drug product is to be used in the treatment of [redacted].

There are four steps for the synthetic route that are conducted to manufacture [redacted] to include:

- Step A: [redacted] is added with HCl and water to form "[redacted]" (known as [redacted]) and coded as [redacted]
- Step B: [redacted] is added with excipients to form "[redacted]) and coded as [redacted]
- Step 1: The addition of [redacted] with excipients such has [redacted] form the non-isolated intermediate, (known as [redacted]).
- Step 2: Excipients are added to the non-isolated intermediate to form the [redacted] API [redacted] and coded as [redacted]

The additional information requested by CDER is documented under "Additional Information" section of this report.

MANUFACTURING CODES

Manufacturing codes are assigned within the firm's SAP system as stated in SOP # HQ.CCO.COP.041.2 EN approved on 09/02/2013. For example, Lot# 19[redacted] represents:

First two digits represents the group number (i.e.:19 = drug product, 17 = API, 16 = exclusive product)

Two Letters represents the customer code (i.e.: [redacted])

Next two digits represent the sequential number of the batch (i.e.: 07 is the seventh batch manufactured for the customer)

Last digits represents the type of product (i.e.: 19 = Spray dry dispersion)

COMPLAINTS

The written procedure entitled, "Handling of Complaints", HQ.CCO.COP029.6EN, Version 6, Effective Date: 04/23/2014 was reviewed.

Complaints are entered into the CAPA system database that is shared with all Hovione sites. Complaints are received usually as an email or letter and QA will be informed of the issue. A Complaint Team is formed with QA and relevant departments. The client will be informed that a complaint has been received and assigned an internal number.

An investigation will be conducted and documented in the Investigation Report to include information, actions, investigations, conclusions, and if root cause found and if impact to quality. Client has an opportunity to provide feedback based on the investigation. Once the complaint report has been agreed upon, the CAPA system has the acknowledgement of the client acceptance and QA will close the complaints. Timeframe to complete the investigation is within 30 calendar days dependent on the nature of the complaint. Once the complaint is closed, the complaint report will be issued to the client.

RECALL PROCEDURES

The firm has a procedure entitled, "Product Recall", HQ.CCO.COP030.1.EN , Version 1, Effective Date: 3/10/11 that was reviewed.

For U.S. recalls, the NDA holder is responsible for the notification to the FDA, as well as monitoring, and closing of the recall. However Hovione, as the API manufacturer will assist as needed.

Mrs.Joana Ferreira verified and informed me that there have been no recalls at the facility.

QUALITY SYSTEMS

Quality System

I reviewed the Quality System program for evaluating out-of-specification results, product and process deviations, validation batches for [redacted] *API and* [redacted] *API* internal compliance audits, and training and customer complaint system. This included reviewing the following procedures:

- SOP # HQ.CCO.COP.014.10.EP, effective on 02/21/2013, "Deviation Records"
- SOP # HQ.CCO.SOP.030.4.EN, effective on 06/27/2014, "CAPA System"
- SOP # HQ.CCO.COP.006.EN, effective on 01/23/2014, "Product Quality Review"
- SOP # HQ.DQ.SOP.098.06.EN, effective on 01/10/2014, "Internal Audit"
- SOP # HQ.CCO.COP.005.4.EN, effective on 09/10/2013, "Internal and External Auditing SOP"
- HQ.QSD.MA.711.2.EN, effective on 03/26/2013, "Quality Agreement between Hovione Farmaciencia SA and [redacted]"
- SOP # QA-046, effective on 10/26/2011, "Qualification Procedure for Auditor"

After I reviewed the documentation and procedures related to the "Quality System", I also evaluated whether the Quality Unit has fulfilled the responsibility of reviewing and approving all procedures related to production, quality control, and quality assurance and assuring the procedures are adequate for their intended use and I did not find any objectionable condition.

Facility and Equipment System

The firm's facility has 18 buildings in total; refer to **Exhibit # RH 1** for the facility layout. The total area of Hovione FarmaCiencia SA Loures facility is 37, 000 m2 with a production capacity of 430 m3 tons. This inspection was focused on Plants # 13C and 15. Plant 13 C is used for the micronization step of [redacted] API and Plant 15 is used for the manufacturing process of [redacted] API. During this inspection, I toured and inspected the surrounding of Plant 13C and 15 to include the warehouse and solvent yard ensuring and verifying that it is totally separated from

both plants. As part of the Facility and Equipment System, I reviewed the purified water system, manufacturing equipment cleaning, pest control and manufacturing equipment calibration and preventive maintenance. I evaluated the following documents:

- SOP # HQ.DQ.SOP099.7EN, effective on 05/09/2014 "Management, Control and Maintenance of the Quality of Water"
- SOP # HQ.WH.SOP032.5, effective on 01/15/203 "Sanitation SOP, Managing Control and Maintenance of Purified Water System"
- P&Id No. 015.0202.010, approved on 10/15/2014 "Piping & Instrument Diagram for Purified Water System"
- Protocol # HQ.QSP.OP013.0EN, approved on 10/12/2005 "Protocol for the Validation procedure of the Purified Water Hoses"
- SOP # HQ.CLN.PL.00301.3 PO, approved on 01/07/2013 "Cleaning Procedure for the Dryer # S-901"
- SOP # HQ.CLN.PL.00495.1 PO, approved on 11/05/2012 "Cleaning Procedure for the Reactor # R-801
- SOP # HQ.CLN.PL.00339.3PO, approved on 02/03/2012 "Cleaning Procedure for the Reactor # RV-4010"
- SOP # HQ.GO.IOP041.4EP, effective on 12/03/2014 "Cleaning and Sanitation of Control Rooms"
- Operational Qualification Protocol for Reactors, Tanks and Precipitators, # HQ.QSP.EQ013.0PO, approved on 08/09/2011.
- SOP # HQ.CLN.PL.00281.A5.0PO, approved on 04/10/2012 "Cleaning Verification Procedure for the Reactor # RV-4010
- Protocol # HE.QSP.EQ026.5 approved on 02/25/2013 "Qualification of the Micronizer [redacted]
- SOP # HQ.QSD.TC.007-A2.1PO, effective on 01/07/2013 "Calibration Procedure for the Temperature Loops
- Protocol for the Operational Qualification of the Glass Lined Reactor RV4010 No. VD/FQ0001, Approved on 04/28/2010
- Re-Qualification Protocol for the Glass Lined Reactor R-801 No. HQ.QSP.EQ.026.3EN, approved on 06/02/2011
- P&Id. No. 015.0202.010, approved on 10/15/2014 "Piping & Instrument Diagram for Purified Water System"
- SOP # HQ.QSD.TC022.3, effective on 12/03/2014 "Procedure for the calibration of reactor level sensor instrument"
- Protocol # QT/FQE001, approved on 06/08/2010 "Installation Qualification of the Double Cone Dryer # S901"

After I reviewed the procedures and documents related to the facility and equipment systems, I found one objectionable condition related to the qualification of the reactors that is further discussed under "Objectionable Conditions Section" Observation # 1.

Production System

Upon arriving to the firm, I requested a list containing all APIs products distributed to the Continental USA since 2013 with their respective client name and shipping date. This list is shown as **Exhibit # 3**. This inspection were focused in the manufacturing processes of [redacted] API and [redacted] API.

I reviewed training of personnel; batch production records and adherence to the evaluation of non-conforming drug products.

I requested the process validation protocol and summary report for [redacted] API [redacted], [redacted] API [redacted]) API manufactured at the facility. I observed that they perform the process validation using three production batches at commercial scale for [redacted] API and three production batches at pilot scale for [redacted].

As previously mentioned in this report, the synthesis of [redacted] involves five steps. Hovione divided the process validation approach in three sections. They issued one protocol and summary report for the step #1, one protocol and summary report for steps #2, 3, 4 and one protocol and summary report for step #5. **Exhibit RH # 5** shows the process flow chart for [redacted] API including the equipment train. Is important to mention that they issued one batch record for each product code during the three manufacturing sections.

I reviewed the following protocols and summary reports for [redacted] API :

Step #1 Product Code: [redacted]

- Process Validation Protocol No. HQ.QSR.PVP120.0EN, approved on 10/25/2012
- Process Validation Summary Report No. HQ.QSR.PV156.0EN,approved on 07/15/2013

Step # 2, 3, & 4 Product Code: [redacted]

- Process Validation Protocol No. HQ.QSR.PVP121.2EN, approved on 05/15/2013(this was a revision of the original version approved on 11/23/2012)
- Process Validation Summary Report No. HQ.QSR.PV160.0EN,approved on 08/06/2013

Step # 5 Product Code: [redacted] (Final Step)

- Process Validation Protocol No. HQ.QSR.PVP122.1EN, approved on 03/22/2013
- Process Validation Summary Report No. HQ.QSR.PV160.0EN,approved on 08/06/2013

Hovione issued a final validation report summarizing all the validation activities conducted for [redacted] API. This report titled "Final Validation Report" No. HQ.QSR.PV163.0 EN was approved on 08/30/2013.

During current inspection, I reviewed the following production batch records for the validation batches of [redacted] API;

Step # 1 Product Code [redacted]

- Batch # [redacted] manufactured on 12/12/2012
- Batch # [redacted] manufactured on 12/15/2012
- Batch # [redacted] manufactured on 12/26/2012

Step # 2, 3, 4& 5 Product Code: [redacted]

- Batch # [redacted] manufactured on 01/27/2013
- Batch # [redacted] manufactured on 02/04/2013
- Batch # [redacted] manufactured on 02/14/2013

Step # 6 Product Code: [redacted] (Final Step)

- Batch # [redacted] manufactured on 03/23/2013 with a batch size of [redacted]
- Batch # [redacted] manufactured on 04/03/2013 with a batch size of [redacted]
- Batch # [redacted] manufactured on 04/03/2013 with a batch size of [redacted]

Yield specification is [redacted]

The certificate of analysis for the final step batches is shown as **Exhibit RH # 6.** The finished API is analyzed for description, identification by ATR and HPLC, water content, heavy metals, residue on ignition, color of the solution, related substances by HPLC, assay by HPLC, content of [redacted] residual solvents, content [redacted], content of [redacted], bacterial endotoxins, total aerobics, total yeast, particle size, optical purity and clarity.

My review of the above mentioned validation protocol, summary reports and batch records did not reveal any objectionable condition.

[redacted] API

During the inspection, I reviewed the registration batches for [redacted] API. As previously mentioned in this report, Hovione FarmaCiencia SA will only perform micronization process to this API. [redacted] API is received and analyzed before it is released for further micrionization process. Once the material is micronized then is analyzed before it is released for distribution.

During current inspection, I reviewed the following batch records for the registration batches of [redacted] API product code [redacted]

- Batch No. [redacted] manufactured on 05/15/2012 with a batch size of [redacted] yield)
- Batch No. [redacted] manufactured on 09/14/2012 with a batch size of [redacted] yield)
- Batch No. [redacted] manufactured on 09/21/2012 with a batch size of [redacted] yield)

Yield specification is [redacted], the above listed batches were placed on stability

The micronizer parameter for the desired particle size is adjusted from [redacted] µm, and then the product is charged into the micronizer and every two hours the micronizer chamber is visually inspected for clogged material.

The certificate of analysis for the micronized batches of [redacted] is shown as **Exhibit RH # 7a.** The finished API is analyzed for description, identification by IR , HPLC and XRPD, heavy metals, water content, residue on ignition, chloride, related substances by HPLC, assay by HPLC, residual solvents by GC [redacted] bacterial endotoxins, total aerobics count, total yeast and mold and particle size. **Exhibit RH # 7b** shows copy of the process flow diagram for [redacted]

My review of the above mentioned validation batch records did not reveal any objectionable condition.

LABORATORY CONTROL SYSTEM

LABORATORY SYSTEM

The following section of this report was written by chemist José A. López Rubet **(JALR).**
The following individuals provided most of the information and records that I requested; and answered the questions that I had.

- Ms. Luisa Paulo, Director of Compliance.
- Ms. Irina Rodrigues, Quality Assurance (QA) Technical Expert, QA Manufacturing.
- Mrs. Cristina Alves, Quality Control (QC) Director.
- Ms. Elisabete Duque, QA Technical Expert, Quality Assurance Development.
- Ms. Maria Carlos, QA Technical Expert, Quality Assurance Development.
- Ms. Alexandra Silva, Director of Analytical Chemistry.

Ms. Luisa Paulo, Director Compliance, Ms Irina Rodrigues, QA Technical Expert, Quality Assurance Manufacturing and Mrs. Cristina Alves (QC Director) accompanied me during the inspection in the laboratory. The laboratories are 17 year old facilities and were located on the third and fourth floors of the building # 15, and second floor of building #13. The complex at Sete Casas, Loures, has two chemical laboratory facilities, one is the QC laboratories and the other is an R&D laboratory located in building # 1 and # 2. The Microbiology laboratory is located on the 2nd floor of the building # 13. The QC Laboratories has 281 square meters.The laboratory performs chemical analysis of Active Pharmaceutical Ingredients, intermediates and starting materials. The laboratory operations appeared orderly and equipped with adequate instruments and equipment to perform their required analysis.

All testing of the drug substan [redacted] for [redacted] (Hovione internal code [redacted]) and [redacted] for [redacted] (Hovione internal code [redacted] Active Pharmaceutical Ingredient (API) were done in the QC laboratories (release of commercial batches) and R&D laboratories (perform validation and registration batches).

The Microbiology laboratory is staffed with 4 analysts, one laboratory assistant and one supervisor who reports to Mrs. Cristina Silva (Laboratory leader). This laboratory analyzes raw materials, finished products and stability samples and operates 6 days a week (Monday to Saturday) with the following shifts: Monday to Friday (8:00AM-5:00PM and 3:00-11:00PM) and Tuesday to Saturday (8:00AM-4:00PM and 3:00-11:00PM). The microbiology laboratory was not completely covered during this inspection due to time constraints and should be covered in more detail during the next inspection.

There is an area in the Chromatography laboratory for the receival of incoming samples, log samples (LIMS software) and storage. The Chromatography laboratory, that analyzes Raw Materials, Intermediates, In-process, Finished products and Stability is under the supervision of Ms. Mónica Barreto, she has 2 technicians and 13 analysts reporting to her. This laboratory is located on the 4th floor of Building # 15 and operates 7 days a week with the following shifts: 1

shift-Monday to Friday (8:00AM-5:00PM), 2-shifts-Monday to Friday (8:00AM-4:00PM and 4:00-12:00PM), and continuous 12h-labor shifts (8:00 AM-8:00PM and 8:00PM-8:00AM).

The Wet Chemistry laboratory that analyzes Raw materials, Intermediates, In-process, Finished products and Stability is under the supervision of Ms. Joana Azuaga. She has 1 supervisor and 8 analysts reporting to her. This laboratory is located on the 3rd floor of Building #15 and operates 7 days a week with the following shifts: 1 shift-Monday to Friday (8:00AM-5:00PM and 4:00PM-12:00PM) and continuous 12h-labor shifts (8:00 AM-8:00PM and 8:00PM-8:00AM).

The stability room area was deactivated and the samples are kept at the premises of a subcontracted company named as BLUESTABIL (3S) – Stability Studies Services, LDA.

The retention samples are located on the 2nd Floor of the Warehouse (Building #8).

In each of the three QC laboratories, the same instruments are used for testing raw materials, intermediates, in-process and finished product samples, as well as stability samples. I verified the instruments used in the analysis of [redacted] that were covered during the inspection.

The instrumentation is not dedicated by product. **Exhibit #: JALR - 1** shows a list of the instrumentation observed in the laboratories and **Exhibit #: JALR – 2** contains the list of instrument used to analyze [redacted] APIs.

I observed that all the laboratory instrumentation was adequately labeled indicating instrument identification and calibration status. The purified water used in the laboratories is obtained from a Milli Q water system SPA08. The control of primary and secondary standards appeared to be adequate. I observed that all reagent containers were labeled showing (among other information) the date it was opened and expiration date. All solutions and reagent preparations that I observed were labeled with the contents, date and the initials of the analyst's name.

I reviewed the general program for calibration/Preventive Maintenance (PM) of laboratory equipment and IQ/OQ/PQ for Karl Fischer, Infrared, HPLC, GC/HS, balances, Powder X-ray Diffractometer (XRPD) and Differential Scanning Calorimeter (DSC) laboratory instrumentation. The laboratory currently uses a LIMS system that was validated in 2001, a CAPA system to manage all non-conforming, CDOC_SPEC to manage the life-cycle of the specifications and others **(Exhibit #: JALR - 3)**. These systems were not completely covered during this inspection due to time constraints and should be covered in more detail during the next inspection.

I reviewed documentation, laboratory reports, and instrument print outs for completeness, accuracy, and adequacy and supervisor oversight; with emphasis on method validations, OOS investigations, stability studies and instrument calibration used for the two NDA covered during the inspection. Deficiencies found during the review of assay/impurity method validation for [redacted] and OOS handling were documented in the objectionable conditions part of this report (**observation # 2 and 3**). I reviewed reports that included analyst's signature and a second person check of the calculations.

During the inspection and laboratory walkthrough, I, Jose A. Lopez Rubet covered the following:

[redacted] for [redacted]) **Active Pharmaceutical Ingredient:**

The Registration and Validation batches for [redacted] drug substance release and stability testing were reviewed for completion. I reviewed the chromatograms, analytical laboratory records, raw data and stability analysis summary reports and no deficiencies were observed. The firm had responded to the minor deviations found during the inspection and data reviewed. The current practices and corrective actions performed appeared adequate for the intended use.

[redacted] for [redacted])

Active Pharmaceutical Ingredient:

I reviewed the methods validation documentation; laboratory reports and instrument print outs (original chromatograms/data) for [redacted] API. Review emphasis was on documents pertaining to method validation, OOS investigations and instrument calibration records and Assay/Impurity analytical methods. The above mentioned documents were evaluated for completeness, accuracy, adequacy and supervisory oversight. The released and stability registration batches reviewed did not contain the chiral analysis. According to management, [redacted], [redacted] API Pharmaceutical development (R&D) department) promised to submit the analytical method to Hovione and perform the test for the commercial batches. The review and evaluation of the chiral analytical test method was not covered during this inspection and should be covered in the next inspection.

The inspection disclosed that: 1) the Laboratory analytical test method validation for Assay/Impurity for [redacted] drug substance release and stability testing was found inadequate for the intended use and 2) the deviation ID: 26014 and CAPA report ID: 27555 for the [redacted] Out Of Specification of the six months stability batch TE-[redacted]-06M-T25H60&T40H75 and TE-[redacted]-06M- T25H60 assay testing was not properly handled. The deficiencies found were discussed under Observation # 2 and # 3 of the "Objectionable Conditions and Management Response" section of this report.

QA/QC Responsibilities

After the review of methods validation, Out Of Specification reports, analytical records, instrument calibration and SOP evaluation; it was found that the QA/QC responsibilities at this facility did not completely perform their quality assurance duties. This inspection disclosed: 1) the Laboratory analytical test method validation for Assay/Impurity for [redacted] drug substance release and stability testing was found inadequate for the intended use and 2) the deviation ID: 26014 and CAPA report ID: 27555 for the [redacted] Out Of Specification of the six months stability batch TE-[redacted]-06M-T25H60&T40H75 and TE-[redacted]-06M- T25H60 assay testing was not properly handled. (See *Objectionable Conditions and Management's Response* section of this report).

Handling of Samples and Standards received (accountability and traceability)

There is an area for incoming samples and standards. After checking the integrity of the samples and the completeness of the accompanying documents (delivery papers, analytical request, Safety/handling instructions, conditions) the request was registered. The samples and standards were

transferred to the appropriate sample storage room. No deficiencies were observed in the handling of samples and standards received and procedures.

Training Records

I reviewed the firm's training procedures and several training records. The firm provides an orientation to new employees and GMP training. No deficiencies were observed in the training records reviewed and Training SOP.

Investigations of Out Of Specification (OOS) and Out Of Trend (OOT)

Since the firm was received two inspections in 2013 and the OOS system was covered. I decided to evaluate the OOS investigation with a CAPA that was closed after these two inspections for the evaluation of the OOS procedure and current investigation practices. Review of the stability deviation ID: 26014 and CAPA report ID: 27555 for the [redacted] Out Of Specification of the six months stability registration batch TE-[redacted]-06M-T25H60&T40H75 and TE-[redacted]-06M- T25H60 assay testing disclosed that the laboratory investigations and CAPA were not handled properly. See observation # 3 in the *Objectionable Conditions and Management's Response* section of this report for more details.

The high OOS and atypical results were obtained for the stability batches on 03/24/2013.

The table # 1 shows the original assay results obtained by the first analyst:

Lot number		Sample 1 (%)	Sample 2 (%)	Specification limit
[redacted]	T25H60 06M (Room	***103.0**	101.4	97.0 % to 102.0 %
	T40H75 06M (Accelerated)	101.5	***102.1**	
	T25H60 06M (Room	***102.1**	***102.1**	
	T40H75 06M (Accelerated)	101.7	101.9	

* Result out of specification limit.

Only the OOS result samples were re-injected (new vial from original samples and re-injection of same vial) on 03/25/13. The results obtained for the same vial re-injection confirmed the original results. Nevertheless, the results obtained for the new vial from the original sample solution did not confirm the original results but still high (except for the lot [redacted] T25H60 06M. The injection of a new dilution from the stock solution is not applicable in this case since the injection sample was taken from the stock solution. The deviation report ID: [redacted] concluded that the root cause was related to homogeneity of the stock samples preparations (dissolution problem).

The table # 2 shows the re-injection assay results obtained by the same analyst:

Lot number	Initial		Re-injection			
	Spl 1	Spl 2	Spl 1	Spl 2	Spl 1	Spl 2
			Same vial	Same vial	New vial	New vial
[redacted]	***103.0**	101.4	***102.8**	Not injected	100.2	Not injected

[redacted]	101.5	*102.1	Not injected	*102.5	Not injected	101.6
	*102.1	*102.1	*102.6	*102.9	101.3	101.5
	101.7	101.9	Not injected	Not injected	Not injected	Not injected

* Result out of specification limit.

At this point, a first re-test was performed by the same analyst on 03/28/13 using the same instrument, column and standard preparations. The data for lot [redacted] T40H75 6M was invalidated after the split of the two samples was found. The test result of 106.1 % was invalidated because it was identified as a d-check (split) failure between samples. The ratio response factors between the 2 sample preparations were found above 2%. The sample result was found outside the specification limit and data result invalidated but was not investigated or noticed until was mentioned during the inspection. The other data results of the three lots were reported as the first re-test.

The table # 3 shows the first re-test assay results obtained by the same analyst:

Lot Number	Initial (03/24/13)		Re-test					
			1 03/28/13					
	Sample		Sample					
	1	2	1	2				
[redacted]	*103.0	101.4	100.8	100.0				
	101.5	*102.1	*106.1	100.4				
	*102.1	*102.1	101.2	100.9				
	101.7	101.9	100.3	100.0				

* Result out of specification limit.

After the first re-test, a new column was ordered since doubt about the column performance and there were no additional columns available for the run. The investigation was stopped until the receiver of the new column. Two additional re-tests for the lots [redacted] T25H60 6M, [redacted] T25H60 6M and [redacted] T40H75 6M and three for the lot T40H75 6M were performed after the column was received. A different analyst and new column received on 05/17/13 was used for these retests run on 05/23/13 and the results were accepted. The average result of the three retests was used for the stability data report of the assay. The original data results for the four lots and the first re-test for the lot [redacted] T40H75 6M were invalidated and the investigation was closed on 07/09/13.

The table # 4 shows the re-tests assay results obtained by a second analyst with a new column:

Batch	Initial		Re-tests					
			1 03/28/13		*2 05/23/13		*3 05/23/13	
	Sample		Sample		Sample		Sample	
	1	2	1	2	1	2	1	2
[redacted]	103.0	101.4	100.8	100.0	99.9	100.3	99.9	100.2
	101.5	102.1	*101.3	*101.7	100.8	99.9	100.5	99.5
	102.1	102.1	101.2	100.9	100.6	100.1	100.8	100.4
	101.7	101.9	100.3	100.0	99.8	100.1	100.5	100.7

* Performed on 05/23/13 with a new column and a second analyst.

The investigation was approved by the Quality Unit without demonstrating that all the batches and batches released during this time period were not affected by a possible deficiency dissolution method procedure during the sample preparations and column performance. Moreover, the CAPA report ID: [redacted] was closed on 04/22/2014 (about one year later from the OOS) without determined the root cause.

Stability Program

Storage of the stability samples was re-located to 3S Bluestabil. The 3S Bluestabil is conracted company that provides stability studies services and is located at Av. Engenheiro Valente Oliveira, lote 19 – Tagus Park, 2780-994 Porto Salvo, Portugal. Hovione is a custom manufacturer, with the customer / contract determining what activities are carried out for the NDA. If the customer requests stability data, stability studies are done, with the samples stored in packages similar to the final packaging, and with the stability chambers located at a service supplier. The samples are removed from the stability chambers at the specified testing points, and sent to the Hovione chemical laboratory for testing.

Contract agreements

The firm uses external contractors for some functions, including storage of stability samples, determination of heavy metals by ICP-MS, Pd by ICP-OES, analytical method validation and government service of sampling and testing (chemical and microbiology) of different types of water used by Hovione. The Quality Agreement and addendums appeared adequate for the intended use. The following Quality Agreement and addendums were reviewed:

1. The Quality Agreement Document dated: 02/25/2014 between Hovione and Bluestabil or 3S - Stability Studies Services for the supply of stability storage services.

2. The Quality Agreement Document dated: 09/17/2014 between Hovione and Solvias AG; Romerpark 2, 4303 Kaiseraugst, Switzerland.

3. The Quality Agreement Document dated: 12/01/2014 between Hovione and "SIMAR-Servicios Intermunicipalizados de Aguas e Residuos dos Municipios de Loures E Odivelas _Divisao de laboratorio e Qualidade – Laboratorio de Aguas".

All the agreements were considered implemented when the final signature is complete. The agreements require the service facility to comply with FDA CGMP regulations as well as several other regulatory requirements. The agreements define which procedures are controlled by Hovione and which are controlled by the service site. The agreements require immediate communication to Hovione for any deviation and Hovione approval of those investigations. Hovione has the right to audit the service site.

Purified Water System monitoring

The firm service contractor collects and analyzes samples for chemical and microbiological (total micro count) testing. I spot checked QC laboratory raw data, trend analysis and all reported results were found to be adequate and within specification limits.

Microbiology Laboratory

This laboratory was not fully covered during this inspection. As mentioned before "SIMAR-Servicios Intermunicipalizados de Aguas e Residuos dos Municipios de Loures E Odivelas _Divisao de laboratorio e Qualidade – Laboratorio de Aguas" performed the service of sampling and testing (chemical and microbiology) of the different types of water used by Hovione. A limited coverage was performed to the microbiological laboratory since it was covered in the previous inspection and no testing was in process during the inspection for the evaluation of the testing process. No deficiency was observed during the microbiology laboratory tour. The observations cited in the last inspection were reviewed and verified during the tour on 12/04/2014.

Retained Samples

I reviewed the retained sample room and sample storage conditions. Samples are stored in a room in building # 8 warehouse freezer AF09 monitored conditions. The samples are labeled with lot number and expiration date. No deficiency was observed in the procedures for the retained samples.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

OBSERVATION 1 (RH)

Your operational qualification of the production reactors located in Building # 15 and identified as R301, R302, R801, RV 4010, R190, R230, R207B, R201, R705, R300 and R208 used for in the

production of APIs, including [redacted], is inadequate in that the RPMs of the impeller shaft rotation from each reactor was never challenged at their current working range. Moreover, the mixing capabilities of them have never been verified or challenged as part of a preventive maintenance program since their initial qualification that have occurred in or around 1997 for the majority of them.

Supporting Evidence and Relevance:

The relevance of this observation is related to the lack of performance verification of the reactors agitation capabilities. The reactors are installed and qualified without measuring the agitation speed (RPMs) of the propellers. Moreover, the current preventive maintenance system that is performed on annual basis does not include the verification of the agitation speed and to challenge them against an acceptance criterion. The manufacturing process contains instructions to adjust the agitation speed of the reactors. This agitation speed is a process parameter established for the manufacturing of APIs.

During the review of the Operation Qualification protocol for reactors, tanks and precipitators, document # HQ.QSP.EQ013.0PO, approved on 8/9/2011, I observed that the verification of the reactor agitator speed was not verified nor challenged against a specification.

Discussion with management:

During the inspection I informed Mr. Nuno Duarte de Almeida that the reactors used in the manufacturing process of [redacted] API were not adequately qualified because the speed of the agitators were not measured nor challenged to assure that they were operating as established and required. I requested the qualification information for the reactors R301, R302, R801, RV 4010, R190, R230, R207B, R201, R705, R300 and R208 and Mr. Duarte de Almeida informed me that they did not performed the agitator speed verification. I also asked Mr. Duarte de Almeida if during the equipment preventive maintenance this parameter is verified and challenged. He responded that they do not verify this parameter as part of the equipment preventive maintenance program. I asked him how they can assure me that reactors installed since 1997 are operating at the required working parameters for agitation. **Exhibit RH # 7c** shows copy of a table containing the initial qualification and re-qualification dates of all reactors before mentioned. He informed me that they will measure this parameter and will check if these reactors still operating at the requested working parameters.

On Thursday December 4, 2014, Mr. Duarte de Almeida and his team measured the agitation speed in rpms for all the reactors above mentioned. The results obtained showed that only Reactors R705 and R201 (this one was not included in the original list of reactors I initially evaluated) did not comply with the agitation speed. Reactor R705 failed the agitation speed in the range of 199 rpms. The tolerance criterion is 199 ± 5rpms and the value obtained was 205 rpms. Reactor R201 failed the agitation peed in the range of 93 rpms. The tolerance criterion is 93± 1 rpm and the value obtained was 53 rpms. Three readings are collected at each range. For Reactor R705 the agitation speed range is from 41 to 199 rpms and for Reactor R201 is from 18 to 93 rpms. **Exhibit RH # 7d** shows copy of the non-conforming calibration records for reactors R705 and R201 respectively.

Mr. Duarte de Almeida initiated two deviations reports to address this out of range values. Deviation report # 37033 was issued for reactor R201 and Deviation report # 37037 was issued for reactor

R705. They both are also shown as **exhibit RH#7d.** Mr. Duarte de Almeida promised to implement the verification of the reactors agitation speed during the operational qualification and during the preventive maintenances.

OBSERVATION 2 (JLR)

Your Quality Unit Failed to establish the specificity of the test method.

Specifically,

Data supporting validation activities performed by your Quality Unit to demonstrate the suitability and adequacy of the analytical test method to be used for the release and stability testing of [redacted] Active Pharmaceutical Ingredient [redacted]) was found to be inadequate in that,

a) Raw data and documents presented by your Quality Unit supporting the validations of the non-compendial Assay and Related Substances analytical test method for [redacted] API do not contain an adequate specificity degradation study due to the presence of an unknown peak (about 10.5 minutes) that co-elute with the main peak of interest (API). Nonetheless, this validation was reviewed and approved by your Quality Unit.

Supporting Evidence and Relevance:

During the review of the [redacted] raw data and documents I observed an unknown peak with the retention time of about 10.5 minutes (Relative Retention Time of 1.08) that co-elutes with the main peak of interest. This peak was not evaluated during the degradation study and no justification for the presence of the peak was included in the analytical test method CRLC4265 validation report (HQ.QSR.MV813.0.EN – CRLC4265-1[redacted] and 1[redacted]: Identification, Assay and Related Substances (by HPLC) – Method Validation Report). See **Exhibit JALR - 4** for the validation report and **Exhibit JALR - 5** for examples of chromatograms reviewed that showed the co-elution of the peaks.

The analytical test method validation evaluation, released/stability data reviewed and inspection/closing discussion disclosed that the firm used two columns for the validation and API testing. The two columns came from the same supplier with the same part number and the same stationary phase packing material however with a different model code [redacted]. According to the supplier and data presented these columns differ with regard to the column end-fitting. The [redacted] designates a column having a threaded column end-fitting while the [redacted] designates a column having a quick seal end-fitting. According management, both type of columns were used in the original method validation study and are being used in the release and stability analysis of the registration batches. I observed and informed to management during the inspection, that they obtained peak co-elution with both columns during released and stability testing of the drug substance.

Discussion with management:

When I asked management about the justification to accept the validation and released/stability raw data obtained with peaks co-elution, management stated that the decision to of accept the validation and data released was taken because this impurity is neither an unknown impurity nor a degradant. According to them, this peak was identified as a process-related impurity by the previous manufacturer. They stated that the origin of this impurity is understood and well-controlled in the current manufacturing process and is not present in the final API at reportable levels. According to them, the peak is not a specified impurity and was not required to be evaluated as part of the selectivity criteria for validation. For that reason the Quality Unit approved the analytical method validation report and determined to be suitable for its intended purpose of batch release and stability testing.

I explained to management that they need to determine and show with validation data documentation the suitability of the method with both columns since the review of the chromatograms showed co-elution of the peaks and no justification was documented. As an example I explained that they need to evaluate the equivalency and degradation performance of the two columns after a prolonged time of use. I explained that they need to define system suitability or resolution criteria to ensure proper separation of the two peaks.

After the explanation and discussions, management decided to repeat the validation of the analytical method and respond in writing to the Agency. They promised to enhance the effectiveness for the forced degradation conditions study, evaluate the performance of the two types of columns to demonstrate their equivalency and define robust system suitability criteria to ensure adequate separation of the two peaks.

It is necessary to mention that the firm presented during the closing a document dated 12/04/14 (**Exhibit JALR – 6**) provided to Hovione by [redacted] The document was discussed during the closing and provided most of the information used during the discussion with the management portion of this observation.

OBSERVATION 3 (JLR)

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,

For the deviation ID: 26014, dated 03/25/2013 and CAPA report ID: 27555 completed on 04/22/2014, your Quality Unit failed to adequately investigate, establish a root cause, or implement corrective and preventive action for the Out Of Specification (OOS) (stability batch TE-[redacted]-06M-T25H60&T40H75 and TE-[redacted]-06M- T25H60) of the

assay testing for [redacted] Active Pharmaceutical Ingredient ([redacted]).

Supporting Evidence and Relevance:

The deviation ID: 26014 (Exhibit #: **JALR- 7**) and CAPA report ID: 27555 (Exhibit #: **JALR- 8**) for [redacted] Out Of Specification (OOS) (six months stability registration batch TE-[redacted]-06M-T25H60&T40H75 and TE-[redacted]-06M- T25H60) of the assay testing was not properly handled. The atypical values and Out-of-specification results and deviations (see **Exhibit #: JALR- 9** for the table prepared by the firm that summarize the OOS results) were not fully investigated and completely resolved by the Quality Unit until they were found during this inspection. The investigation did not extend to other batches that were prepared and run by the same analyst using the same analytical test method and/or other batches tested using the test method procedure that was declared to be deficient.

Only the OOS result samples were re-injected (new vial from original samples and re-injection of same vial) during the laboratory investigation on 03/25/13. The deviation report ID: 26014 concluded that the root cause was related to homogeneity of the stock sample preparations (dissolution problem). Nevertheless, the re-injection did not confirm the original results.

At this point, a first re-test was performed by the same analyst on 03/28/13 using the same instrument, column and standard preparations. The data for lot [redacted] T40H75 6M was invalidated after the split of the two samples was found. The sample result was found outside the specification limit and data result invalidated but was not investigated or noticed until it was mentioned during the inspection. The other three lots data results were reported as the first re-test.

After the first re-test, a new column was ordered because doubt about the column performance and there were no additional columns available for the run. The investigation was stopped until the receipt of the new column. A different analyst and new column (received on 05/17/13) was used for these retest runs on 05/23/13 and the results were accepted. The average result of the three retests was used for the stability data report of the assay. The original data results for the four lots and the first re-test for the lot [redacted] T40H75 6M were invalidated and the investigation was closed on 07/09/13.

The table shows all the results obtained during the investigation:

The table shows all the results obtained during the investigation:

Batch	Initia l		Re-injection (03/25/13)				Re-tests					
			Same Vial		New vial		1 03/28/13		*2 05/23/13		*3 05/23/13	
	Sample		Sample		Sample		Sample		Sample		Sample	
	1	2	1	2	1	2	1	2	1	2	1	2

[redacted]	103.0	101.4	102.8	Not injected	100.2	Not injected	100.8	100.0	99.9	100.3	99.9	100.2
	101.5	102.1	Not injected	102.5	Not injected	101.6	*101.3	*101.7	100.8	99.9	100.5	99.5
	102.1	102.1	102.6	102.9	101.3	101.5	101.2	100.9	100.6	100.1	100.8	100.4
	101.7	101.9	Not injected	Not injected	Not injected	Not injected	100.3	100.0	99.8	100.1	100.5	100.7

* Performed on 05/23/13 with a new column and a second analyst. Limits: 97.0 % to 102.0 %.

The investigation was approved by the Quality Unit without demonstrating that all the batches, including the batches released during this time period, were not affected by a possible deficient dissolution method procedure during the sample preparations and column performance. The analyst who performed the original tests and several retests/re-injections was not a new employee and had received the training in this specific analytical test method and OOS procedure. Other batches performed by the same analyst after this investigation were not questioned and batches run within this sample run set were released.

In addition, as part of the investigation and to understand what should be the stabilization time and dissolution problem of the samples before the injection, the firm performed one study (see CAPA report ID:27555 issued on 06/14/13), where previous stability samples were injected after 5, 10, 20 and 30 minutes of preparation.

Lot number	5 minutes	10 minutes	20 minutes	30 minutes
[redacted]T25H60 09M	98.1 %	100.6 %	100.2 %	98.5 %

All the results obtained were found within specifications and did not conclude or confirm that the homogeneity or dissolution was the problem for OOS results obtained during the OOS investigation deviation ID: 26014. Nevertheless, the CAPA report ID: 27555 was closed on 04/22/2014 (about one year after the OOS) without determining the root cause. The corrective actions for the investigation report did not present concrete actions to permanently resolve the assignable cause for the OOS results. The corrective actions only addressed the stability data disposition and not the root cause.

It is necessary to mention that the laboratory analytical method CRLC4265 used for these tests was a validated method, but was found inadequate during this inspection (see observation # 2). According to management the validation was done by the R&D and all the parameters passed the acceptances criteria.

Discussion with management:

When I asked management about the rational to conclude that the sample dissolution was the problem when they obtained high results for the samples, management did not understand my

request. They responded that they followed the OOS procedure during the investigation. I explained to management and those present during the discussion of this issue that if they claimed a problem with the sample dissolution, the results obtained were supposed to be lower since less quantity of sample was dissolved.

I explained that the firm invalidated the atypical and OOS results based on a preliminary investigation that questioned the analytical test method sample preparation procedure and column performance. Nevertheless they accepted the conformance results obtained for other batches in the same HPLC run performed by the same analyst, same column and same analytical method sample preparation procedure. I explained to management that they cannot state that the dissolution technique or sample preparation was the cause of the out specification results when they are using a validated Analytical Test method and the analyst received an adequate training. Their response was that they followed the OOS procedure during the investigation. According to them, the OOS procedure provided for the retest of the samples. I mentioned to them, that the preliminary assessment (sign/date by the analyst and supervisor) showed that the analyst followed the test procedure without any deviations. I explained that for example, they compromised all the batch samples prepared by the analyst when they established that the analyst technique or dissolution process or column was the root cause. They agreed with my explanation.

I explained that they cannot be selective and affirm that the situation is only applicable to some of the sample preparations or column performance without any scientific justification and documentation of the rational in the investigation. I mentioned that they are supposed to extend the investigation to the other batches prepared using the same method and column and determine if these batches were affected by the established conclusion or if the analyst does not follow the analytical procedure as they stated during the interview. They understood the concept and the importance of verifying the method validation, follow an adequate OOS procedure, and validate or fix the problem found prior to starting this kind of justification in an atypical/OOS investigation. After the explanation they agreed with the observation and promised to investigate, improve the CAPA system and investigation procedure.

Additional Information

The firm's written response was received on 12/27/ 2014, and appeared to be adequate when fully implemented.

Voluntary Corrections

The firm's general discussion with management items for the inspection on 09/23-27/13 were reviewed and verified on 12/04/2014. This inspection found that the firm had responded completely to all the items.

REFUSALS

There were no refusals encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

On 12/05/2014, we issued the form FDA-483 "Inspectional Observations" to Mr. Nuno Duarte de Almeida, Plant General Manager. At the conclusion of the inspection, we held a closing meeting with Mr. Almeida, to discuss the inspectional observations. Other firm's management personnel present during the closing meeting were:

- Guy Villax,
- Alvaro Lopes
- Mario Rodrigues
- Elisabete Duque
- Luis Egadaes
- Nuno Rebelo
- Luisa Paulo
- José Lisboa
- Joana Ferreira
- Alexandre Sardinha

Copies of FDA-483 were made for the team management present in the meeting. Mr. Almeida and the rest of the firm's representatives spent some time reading the document.

After reading the document, time was given to make some clarifications on the observations listed in the form. All observations were fully explained to firm's officials and discussed with them throughout the inspection as well.

As previously indicated in this report, I conducted daily meetings with firm's management prior to close the inspection to discuss any concerns and/or observations, and gave them ample opportunities to present me any additional information in order to clarify and/or to resolve the issues and observations.

In general, firm's management agreed with the observations that were fully discussed during the exit meeting.

Mr. Almeida, General Manager, indicated that a written response will be sent to FDA CDER and SJN-DO within the next fifteen (15) working days.

I warned the firm's officials that the objectionable conditions listed in the form FDA-483 may, after further review by the Agency, be considered to be violations of the FD&C Act and that regulatory actions, including warning letter and refusal for entry to the USA of goods shipped by the firm, were available to FDA if establishments do not voluntarily correct serious conditions. I also explained them that the information I reviewed during the inspection was limited and that the Quality Unit is responsible to assure full compliance with the cGMPs and the FD&C act.

I thanked Mr. Almeida and his staff for their time, cooperation and professionalism during the inspection. No further discussion was held and the inspection was ended.

ADDITIONAL INFORMATION

Logistics and Accommodations

Hotel accommodations was at Marriott, Lisboa. This hotel was within per diem with the current exchange rate. The hotel have WiFi only in the lobby and business center. This hotel is close to the city center and was within walking distance to restaurants. The firm provided transportation to/from the facility to the hotel on a daily basis.

[redacted] Spray Dried Dispersion (additional information requested by CDER during the inspection)

- Review and verify adequacy of the in-process controls, sampling plan and testing of the finished product- [redacted] SDD for a batch disposition.

In-Process control were established and challenged with the specifications set for IPCs. **Exhibit RH # 8** shows copy of the in-process test conducted to [redacted] DDS. Due to time limitation I was not able to cover in details the adequacy of the in-process controls.

- Review and verify adequacy of available process validation plans, reports and/or continued process verification (CPV) reports for [redacted] SDD since last inspection.

Due to time limitation I was not able to cover in details the adequacy of the process validation plans and continue process verifications.

- Report on any deviation, or OOS if observed for [redacted] SDD.

I collected the annual product review for [redacted] SDD batches manufactured during 2013. They manufactured a total of [redacted] batches being all released with no OOS. However they issued [redacted] manufacturing deviations with only 1 being classified as critical. The deviation was described as "feed pressure and outlet temperature out of PAR/DSL on SD step. They conducted an investigation and determined that the assignable cause was operator lacking of training. Batch # HQ00032 was classified as a research batch. **Exhibit RH # 9** shows copy of [redacted] SSD APR for 2013

- Report on adequacy of investigation(s), management of associated CAPAs and change control procedures.

I reviewed the investigations, CAPA and change control procedures and did not observed any objectionable conditions.

- In addition to other intended quality attributes (e.g., assay, impurities, moisture), ensure that particle size of [redacted] SDD is measured and reported on the certificate of analysis (COA) for each batch shipped to [redacted]

I reviewed the release specifications of the [redacted] SDD and collected copy of the same that is included as **Exhibit # 10.** Particle Size test is not listed in the specifications nor performed for Ivacaftor. I also collected one Cof A for [redacted] SDD lot # HQ00041 that is shown as **Exhibit RH # 11** showing no particle size test.

- Review Hovione's Quality agreement [redacted] and verify whether the established procedures are sufficient to share relevant product knowledge and quality information for [redacted] SDD in a timely manner between the two (quality management) organizations.

I reviewed the Quality Agreement between Hovione [redacted] and found that the same contains an statement where [redacted] will provide product specific technical support as reasonably requested by Hovione (page 14 of 18, section 3.17). After I reviewed the quality agreement I did not find any objectionable condition. **Exhibit RH # 12** shows copy of the Quality Agreement between [redacted] and Hovione, Document # QAgr-005 approved on 02/20/2014

SAMPLES COLLECTED

No samples were collected during this inspection.

VOLUNTARY CORRECTIONS

The firm promised to voluntarily correct the objectionable conditions listed in the FDA 483 form.

EXHIBITS COLLECTED (RH / JALR)

Exhibits collected by Investigator Ramon Hernandez are identified as "**RH**" Exhibits obtained by Chemist José A. López Rubet are identified as "**JALR**".

RH-1	Hovione FarmaCiencia SA Facility Layout
RH-2	Copy of the firm registration and drug product listing
RH-3	List of all products manufactured at the site and shipped to the continental USA since 2012
RH-4	Copy of the organizational charts of Hovione FarmaCiencia SA
RH-5	Production process including equipment train for the manufacture of [redacted] API

RH-6	Certificate of Analysis for [redacted] API Validation Batches
RH-7a	Certificate of analysis for [redacted] micronized batches
RH-7b	Copy of the process flow diagram for [redacted]
RH-7c	Table containing the initial qualification and re-qualification dates of all reactors
RH-7d	Copy of the non-conforming calibration records for reactors R705 and R201 respectively and Deviation reports # 33033 and 33037.
RH-8	Copy of the in-process test conducted to [redacted] DDS
RH-9	Copy of [redacted] SSD Annual Product Review for 2013
RH-10	Copy of the release specifications for the [redacted] SDD
RH-11	Certificate of analysis for [redacted] SDD lot # HQ00041
RH-12	Copy of the quality agreement between [redacted] and Hovione, Document # QAgr-005 approved on 02/20/2014

JALR - 1	List of major QC laboratory instrumentation (3 pages both sides).
JALR - 2	List of laboratory instrumentation used to evaluate the product (2 pages both sides).
JALR - 3	Copy of the computerized system description (1 page).
JALR - 4	Copy of the analytical test method CRLC4265 validation report (21 selected pages of 52 pages)
JALR - 5	Copy of some examples of chromatograms reviewed that showed co-elution of peaks (27 selected pages of 103 pages).
JALR - 6	Copy of the [redacted] document dated 12/04/14 provided to Hovione (7 pages).
JALR - 7	Copy of the deviation ID: 26014, dated 03/25/2013 (6 pages).
JALR - 8	Copy of the CAPA report ID: 27555 completed on 04/22/2014 (12 pages).
JALR - 9	Copy of the table that summarizes the OOS results (4 pages).

ATTACHMENTS

FDA 483 "Inspectional Observations Form" issued to Mr. Nuno Duarte de Almeida, Plant General Manager, on 12/05/2015.

Ramon Hernandez, Investigator

Jose A. Lopez Rubet, Chemist