DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
629 Cranbury Road
East Brunswick, NJ 08816

February 8, 2016

Marco A. Gil PhD, General Manager
Hovione, LLC
40 Lake Drive
East Windsor, NJ 08520

Dear Dr. Gil,

We are enclosing a copy of the establishment inspection report (EIR) for the inspection conducted at your premises at the above address on December 3rd, 2015 through December 16th, 2015 by Investigator Maria Estrella on behalf of the U.S. Food and Drug Administration (FDA). When the Agency concludes that an inspection is "closed," under 21 C.F.R. 20.64 (D) (3), it will release a copy of the EIR to the inspected establishment. This new procedure is applicable to EIRs for inspections completed on or after April 1, 1997. For those inspections completed prior to the above date, a copy of the EIR may still be made available through the Freedom of Information Act (FOIA).

The agency is working 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 FOIA and 21CFR Part 20. This, however, does not preclude you from requesting and, possibly, obtaining any additional information under FOIA.

If there is any question about the released information, feel free to contact:

Louise Miranda
U.S. Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, New Jersey 07054
Telephone: 973-331-4903

Sincerely,

Meyer J. Slobotsky
Supervisory Consumer Safety Officer

MJS:gjp
Attachment

Establishment Inspection Report	FEI:	**3006106736**
Hovione LLC	EI Start:	12/3/2015
East Windsor, NJ 08520-5321	EI End:	12/16/2015

TABLE OF CONTENTS

SUMMARY

A routine cGMP inspection of this manufacturer of active pharmaceutical ingredient (API) was performed as per NWJ-DO FY16 Workplan, under FACTS Assignment 11592529, OP ID 9396. Inspectional guidance was provided by CPGM 7356.002, Drug Manufacturing Inspections; 7356.002F, Active Pharmaceutical Ingredients; and Guidance for Industry titled "Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients."

The previous inspection was conducted 04/23-26/2013, and was classified NAI. Coverage of the Quality, Production, and portions of the Facilities and Equipment and Laboratory Control Systems was performed. The site was found to be solely producing one marketed drug substance, [redacted] for one US customer, [redacted] No FDA 483, Inspectional Observations, was issued. Few items were discussed with management during the inspection, which included the following: undefined extended timeframes were utilized to identify an unknown impurity and complete an appropriate corrective and preventive action, following an OOS result in an intermediate of the [redacted] process; qualification activities are not performed after moving the ISO-8 hood used for packaging the final product; it is unclear if a validated method allows for contact and settling plates used in environmental monitoring can be inoculated (sampled) and stored

at refrigerated conditions over the weekend prior to shipping and incubation by the contract laboratory the following week, as was noted in a deviation report; and the cleaning procedure for the multi-purpose containment hood used to sample the starting material does not adequately address the full range of materials sampled by the primarily R&D facility.

The current inspection covered the Quality, Production, Laboratory Control, and portions of the Packaging and Labeling Systems. The firm was found to continue manufacturing operations of APIs for commercial distribution, research and development, and clinical phase projects for various customers. The firm now manufactures two commercial APIs, [redacted] and plans to expand their API inventory. Corrections regarding previous inspectional findings were reviewed. A FDA 483 was issued for lack of controls in the distribution of laboratory worksheets. Additional items were also discussed with management regarding control of profiles in LIMS, stability studies for API intermediates, evaluation of CAPAS and testing methods.

There were no refusals encountered and no samples were collected. Their drug registration was current.

ADMINISTRATIVE DATA

Inspected firm:	Hovione LLC
Location:	40 Lake Dr East Windsor, NJ 08520-5321
Phone:	609-918-2600
FAX:	609-918-2615
Mailing address:	40 Lake Dr East Windsor, NJ 08520-5321
Dates of inspection:	12/3/2015-12/4/2015 , 12/7/2015, 12/9/2015-12/11/2015 , 12/16/2015
Days in the facility:	7
Participants:	**Maria Estrella, Investigator**

On 12/3/2015, I, CSO Maria E. Estrella, presented my credentials and issued a FDA 482, Notice of Inspection, to Marco A. Gil, General Manager, who stated was the most responsible person for the site. I explained the purpose of the visit was to conduct a surveillance cGMP inspection of the facility.

A closeout meeting was held on 12/16/15. The following were present: Marco A. Gil; Jenny Fong, Head of Compliance; Nuno Rodrigues, Release Group Leader; Andrea Cruz, Quality Assurance Manager; Dirce Macario, Head of Process Engineering; and Bhavyata Patel, Quality Assurance Specialist. A FDA 483, Inspectional Observations, was issued to Mr. Marco A. Gil. Management committed to provide a written response within 15-business days to the NWJ-DO. No samples were

collected and no refusals were encountered.

Official correspondence should be address to:
Marco A. Gil, *General Manager*
Hovione LLC
40 Lake Drive
East Windsor, NJ 08520
mgil@hovione.com

HISTORY

The Establishment Inspection Report (EIR) from inspection ended on 5/2/2011 details the firm history. Additionally, management provided and overview presentation for Hovione and the New Jersey site **(Exh. 1)**. The NJ site was founded in 2002 and is one of the five API manufacturing facility located throughout the world under the name Hovione. Hovione also has office sites internationally located.

This site employs 56 people and operates Monday through Friday from 8:00 am to 5:00 pm. The firm's drug manufacturing registration is current.

Changes since the last inspection include the manufacturing of API [redacted] for a recently approved NDA, in September 2015, for customer [redacted] Additional changes since the last inspection regards to personnel and is noted below.

- David Hoffman, former President-US Operations, Vice president Exclusives Business Unit, is now VP of sales. He was not present during this inspection.
- Marco A. Gil, Ph.D. is the new the General Manager, since approx. July of 2015. Michael D. Ironside previously held this position.
- Dirce Macario, former Head of Compliance, is now the Head of Process Engineering.
- Jenny Fong is the new Head of Compliance, since approx. April 2015.
- Filipe Tomas, former head of Process Engineering, is now the Expansion Manager.
- Anthony DiSanti is the new Process Engineer, who formerly was Dhvanit Patel.

Mr. Gil reported they have plans to expand the facility and product inventory. However, they have not initiated construction and are working on the extension plan for the facility.

INTERSTATE COMMERCE

This site manufactures two APIs [redacted] 17PA03 and [redacted] 17TR68) that are distributed 100% into interstate commerce. [redacted] is manufactured for US customer [redacted] and is shipped to their warehouse located in [redacted]. [redacted] is manufactured for US customer

[redacted] located in [redacted]. Product is shipped via USP [redacted] or World Courier [redacted].

JURISDICTION
This firm manufactures API for further processing to produce finished drug products.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED
Mr. Marco A. Gil provided a company overview presentation that includes the firm's organizational chart **(Exh. 1, pg. 9)**. Ms. Jenny Fong, head of Compliance, provided the organizational chart for the Quality Unit at Hovione, NJ **(Exh. 2)**. Ms. Dirce Macario, Head of Process Engineering, provided information regarding the responsibilities of the below employees that actively participated during this inspection. Ms. Macario and Ms. Fong were the main contacts during this inspection.

Marco A. Gil, Ph. D., General Manager, is responsible for all operational decisions at the East Windsor, NJ facility. He was transferred from the Hovione Portugal site to the East Windsor facility, this year. Mr. Gil reports directly to Luis Gomes, Vice President Manufacturing, and Filipe Gaspar, Vice President R&D, who are both located at the Loures, Portugal site.

Jenny Fong (Shun Yin), Head of Compliance, is responsible for all activities of the Quality Unit such as change control, deviations, product quality reviews and procedures. She provided documents and assisted with questions during the inspection. Ms. Fong reports to Joao Alves, Director of QA in Loures, Portugal site, and to Marco A. Gil, General Manager. Ms. Fong was transferred from Macau, China site this year.

Dirce Macario, Head of Process Engineering, is responsible for the manufacturing of batches, logistics, approval of batch production records, training of production employees, the Process Engineers, Operations, Facilities and the Warehouse Departments. During the inspection, she provided documents, and assisted with questions. Ms. Macario directly reports to Mr. Gil.

Anthony DiSanti, Process Engineer, is responsible and directly involved in each step of the process to manufacture [redacted]. He assisted with the process flow for both products. He reports to Ms. Macario.

Andrea Cruz, Quality Assurance Manager, is responsible for preparing and reviewing Quality Unit related documentation. Ms. Cruz reports directly to Ms. Fong.

John Rose, Materials & Planning Specialist, is responsible for receiving materials into the firm's warehouse and into SAP, sampling, labeling, and storing the materials into the warehouse. He assisted with explanations related to warehousing, sampling, packaging, and labeling activities.

David Storey, Head of Analytical Development & Project Manager, is responsible for methods

development and validation. He assisted with method validation for the impurities in [redacted] and [redacted] He reports to Mr. Gil.

Nuno Rodrigues, Release Group Leader, is responsible for performing laboratory tests, reviewing data, and producing certificates of analysis. Mr. Rodrigues reports to Ms. Fong.

MANUFACTURING/DESIGN OPERATIONS

This firm manufactures APIs for commercial use, clinical trials, and for research and development. Mr. Gil explained that Hovione is a contract development facility. They provide technology knowledge for their customers regarding API or other products synthesis at various scales and stages.

Their manufacturing operations have not changed since the last inspection. They have been manufacturing [redacted] since approximately 2008 for [redacted], and received approval to manufacture [redacted] in September 2015 for [redacted] is shipped to Hovione Portugal site for micronization prior to being distributed to its customer; the micronized product is the commercial API product.

During this inspection, the Quality, Production, Laboratory Control, and portions of the Packaging and Labeling Systems were covered. As part of the system coverage, the following areas and documents were reviewed for [redacted] products: selected deviations and OOSs since previous inspection thru December 2015; manufacturing areas and products synthesis; SOPs; Change Controls; qualification of reactor RX-0202 (used in the preparation of [redacted]; packaging and labeling operations (labeling is generated as needed); QC laboratory controls; method validation for related compound testing; process validation for [redacted] API; and [redacted] validation batch records.

Deficiencies noted are described in the Objectionable Conditions and Management Response, and General Discussion with Management sections. Management promised corrective actions to the deficiencies noticed in the FDA 483 and items discussed. See the *Objectionable Conditions and Management Response*, and the *General Discussion with Management* for more details on items covered and discussed with management.

MANUFACTURING CODES

The firm continues to use the same manufacturing codes. This consists of a material number (e.g., 17PA03 for [redacted] and 17TR68 [redacted], and a two-part alphanumeric batch number (two letters identifying the facility, followed by a sequential five-digit number generated by the inventory control system, SAP, e.g. NJ00007).

A material number starting with 17 refers to a finished product while a material number starting with 16 refers to an API intermediate.

COMPLAINTS
Ms. Dirce Macario, Head of Process Engineering, reported they have not received complaints since the last inspection.

RECALL PROCEDURES
The firm have not been involve in any recall since the last inspection.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483
OBSERVATION 1

Procedures are not in writing and/or fully followed:

Specifically, details of laboratory analyses, such as sample and standard preparation, calculations, and results for APIs and/or intermediates [redacted] are captured on printed data sheets that can be printed multiple times by the analysts. There is no assurance that the generation of these documents is appropriately controlled.

Supporting Evidence and Relevance/Discussion with Management:
The firm does not have adequate laboratory controls or procedures to ensure the issuance of analytical worksheets is controlled. The firm records analytical data generated from APIs, intermediates and raw material testing in data sheets. The data sheets are fillable version of the testing method and include sample and standard preparations details, as well as calculations and testing results.

Mr. Nuno Rodrigues, Release Group Leader, described the process followed by the analysts once they are assigned a sample for testing. Analysts enter the assigned sample number in LIMS and obtain the methods required for the sample analysis. An analysis request example is provided in **Exh. 3**. The required methods for the sample analysis are then obtained from Doc Stream (electronic system for document control); an example is shown in **Exh. 4**. These fillable methods indicate the date and time are printed out, but multiple copies can be printed at the time. There is no assurance that the generation of these documents is appropriately controlled.

On 12/9/15, I demonstrated to Ms. Macario, Ms. Fong, and Mr. Rodrigues that there is no control for the distribution of analytical worksheets and that multiple copies can be printed out at the time. I also mentioned the forms could be photocopied. An example of an empty fillable form for [redacted] is included as **Exh. 5** and **Exh. 6**, respectively. A completed worksheet for [redacted] lot 17PA03.NJ00052 is included as **Exh. 7**, and for [redacted] intermediate 16TR68030.NJ00007 is included as **Exh. 8**.

Management acknowledged the observation and implemented corrective actions that were verified during the closeout meeting (see the Voluntary Corrections section). Additionally, Ms. Macario stated that testing methods were changed to a fill-in format early this year. A written response to this observation will also be provided to the NWJ-DO within 15-bussiness days.

REFUSALS

No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT

1. While covering the security controls for laboratory data, the release group leader (QC department) described how results are approved in LIMS. LIMS is the laboratory control system that generates certificate of Analyses and communicates with their inventory system, SAP, for product status such as approvals.

   He explained that the QA approves release of finished products in LIMS and the peer review team from QC approves the release of raw materials and intermediates. I discussed that this distinction was not clearly identified in their SOP HQ.CCO.COP017.5.EN **(Exh. 9)** and that there were no controls in the system to prevent QC from releasing finished products in LIMS.

   The approval of release products in LIMS (intermediates, raw material and finished products) associated with [redacted] was reviewed from April 2013 to December 2015, and no deficiencies were noted. The authorized personnel were noted to have released the appropriate materials in LIMS.

   However, I discussed with management that they should have controls to ensure that only authorized personnel released the material in LIMS. Mr. Rodrigues reported that analyst and QC personnel are trained to know that only QA releases finished products in LIMS. Raw material and intermediates records are reviewed and approved by QC. Finished products are reviewed by QC, but approved for release, in LIMS, by QA. During the inspection, the firm provided change control 7009 "under implementation" status to update the profiles functions in LIMS for the analysts and QA personnel in harmonization with all the Hovione sites. The change control was opened in 4/24/2015, but was not yet implemented.

2. The firm does not have stability studies for API intermediates and these are assigned a 12-month re-test period according to procedure HQ.CCO.COP020.2.EN **(Exh. 10)**. I discussed that if intermediates are retained for extended periods of time, they should have stability data to support the hold time period.

   I requested a re-test period assessment for the intermediates of [redacted] that were held for long periods of time and also a table for each product that include the time the

intermediates were held prior to be used in the manufacturing of the sequential step or related intermediate.

Ms. Macario provided an assessment for [redacted] intermediate 16PA03020 and 16PA03035 **(Exh. 11)**. According to her and the process, these intermediates can be held for extended periods of time for use as seeds or in the sequential manufacturing step. However, the assessment was based on chromatographic data for [redacted] standards used in the laboratory, which are not representative of the storage conditions of the materials. According to a table provided by Ms. Fong **(Exh. 12)**, which includes the intermediates used in batches of [redacted] manufactured in 2014 and 2015, intermediate 16PA03020 has been held for as long as 372 days; 16PA03035 has been held for as long as 476 days; and 16PA03040 has been held for as long as 333 days. It was noted the intermediates were retested according to the assigned retest period and a retest period of six-months was assigned for [redacted] intermediates.

Ms. Macario provided an assessment for [redacted] intermediates 16TR68030 and 17TR68 **(Exh. 13)**. According to her and the process, these intermediates can be held for extended periods of time for use as seeds or in the sequential manufacturing step. However, [redacted] intermediates 16TR68020 can also be used as seeds in the manufacturing of 16TR68020 intermediate or for manufacturing intermediate 16TR68030, but it was not included in the assessment provided.

The assessment provided by Ms. Macario to justify a 12-month re-test date for [redacted] intermediates 16TR68030 and 17TR68 is based on the formal on-going stability program for the commercial API 17TR68M (micronized 17TR68 material). 17TR68M was considered for the re-test date assessment because it reflects the worst-case situation relatively to materials 16TR68030 and 17TR68, due to higher surface area exposure.

Current stability data for 17TR68M supports up to 30 months (Hovione Portugal site) and customer [redacted] has stability data for up to 24-months for intermediate 17TR68 (unmicronized API). I discussed that each intermediate should be place on formal stability studies to generate data that supports prolonged hold times.

According to a table provided by Ms. Fong **(Exh. 14)**, which includes the intermediates used in all [redacted] manufactured batches, intermediate 16TR68020 has been held for as long as 240 days for the next manufacturing step, and for over 365 days for use as seed; 16TR68030 has been held for 30 days prior to be used in the next manufacturing step, and for over 365 days for use as seed; and 17TR68 has been held for up to 73 days prior to be used in the following manufacturing step. It was noted the intermediates were retested according to the assigned retest period.

Management discussed they will evaluate formal stability studies for intermediates held for long periods in the manufacturing of commercial APIs.

3. Not all validation batches are place on stability. The firm initiated formal stability studies for [redacted] intermediate 17TR68 during process validation. 17TR68 is the final intermediate produced at the Hovione NJ site. 17TR68 is shipped to Portugal Hovione site for micronization. The firm manufactured three validation batches of 17TR68 (17TR68.NJ00005, 17TR68.NJ00006 and 17TR68.NJ00007); however, only one validation batch was placed on stability (17TR68.NJ00005).

   Also, sequential intermediates towards the synthesis of 17TR68.NJ00005 were not place on stability. Intermediates were randomly selected during the manufacturing of the three validation batches. For example, intermediates 16TR68020.NJ00008 and 16TR68020.NJ00009 were used to manufacture 16TR68030.NJ00005. Intermediate 16TR68030.NJ00005 was used to manufacture 17TR68.NJ00005. However, intermediates 16TR68020.NJ00008, 16TR68020.NJ00009, and 16TR68030.NJ00005 were not place on stability. The correlation between manufactured batches and batches on stability is included as **Exh. 15**. I said they should include all validation batches on stability and/or all the intermediates involved in the preparation of each final material in order to have meaningful data for each stage of the process.

   Deviation report 42747 was reviewed and described an OOS results for intermediate 16TR68030.NJ00007 at 3-month station for major unspecified impurity (Spec. NMT 0.15%, result 0.17%) **(Exh.16)**. However, the intermediate generated from 16TR68030.NJ00007 and 17TR68.NJ00007 (non-micronized finished product obtained from recrystallization of 16TR68030.NJ00007), was not selected for stability studies.

   The investigation above appears adequate and a CAPA was opened to continue evaluating the impact of the results (e.g. monitoring stability of micronized API 17TR68M.NJ00007 manufactured with 16TR68030.NJ00007 and placing additional lots of the above intermediate on stability). Management/investigation discussed that testing results for 17TR68.NJ00007 and trending results for 17TR68 indicate the above impurity is removed during the recrystallization step.

   I discussed they should evaluate a shorter re-test period for this intermediate and evaluate the capability of the recrystallization step to remove the impurity found at 3-month station (approx. at RRT 0.27). Management acknowledged my observation and provided change controls to assign a new re-test period of 12-days to the above intermediate 16TR68030 **(Exh. 17)**. Stability data for all the validation batches for the finished micronized API 17TR68M and intermediates selected for stability were reviewed and no deficiencies were noted. The firm continues to monitor stability of 16TR68030.NJ00007 and additional information is generated to determine if

content [redacted] may have an impact on the product. Moreover, additional lots of intermediate 16TR68030 will be place on stability to gather more information.

4. CAPA report 22087 **(Exh. 18)** was not adequately evaluated prior to its closure. This CAPA was opened following Deviation Report 13458 **(Exh. 19)** due to an OOS result obtained during related compound testing of [redacted] intermediate 16PA03035.

   This CAPA, issued on 9/14/2012, was opened to revise the analytical testing method used to test purity and related substance in [redacted] intermediate 16PA03035 due to an impurity formed *in-situ* during standard and sample preparations and described not to be a process related or degrading impurity at approximately RRT 1.10.

   The impurity was identified via LC-MS during investigation report 13458, closed on 10/26/2012, and the method was updated to include sonication controls during the standard and sample preparations (time limit and level of water bath for sonication). Upon changes to the testing methods, two batches were manufactured yielding results within specification, but close to the higher end of the specification range for the major unspecified impurity: 16PA03035.NJ00032 (1.7%) and 16PA03035.NJ00033 (1.5%); the major unspecified impurity specifications are NMT 2.0%. These results were used to determine the effectiveness of the CAPA and closure on 4/24/2013 **(Exh. 18)**.

   On 6/30/2014, deviation report 33953 **(Exh. 20)** was created due to OOS result obtained for batch 16PA03035.NJ00041 (Results: 3.063% and 2.943%) for the major unspecified impurity at approximately RRT 1.10. As a result, the analytical testing method was evaluated and revalidated using [redacted] as diluent for samples and standard preparations as per CAPA 34615 **(Exh. 21)**. I discussed that evaluation of the method should have occurred after proper evaluation of results obtained for batches 16PA03035.NJ00032 and 16PA03035.NJ00033 noted above.

   Ms. Macario discussed that even though CAPA 22087 was closed, its the effectiveness continued to be evaluated in the 2013 PQR (Product Quality Review) as reported in the corresponding CAPA, which considered evaluating and revalidating the analytical testing method using [redacted] as diluent. Additionally, testing results obtained for batches manufactured after 16PA03035.NJ00032 and 16PA03035.NJ00033 (approximately five batches) demonstrated the sonication controls, noted in the testing method, proved effective until the OOS result reported in deviation report 33953. Results reported for the impurity at RRT 1.10 and the method version are summarized in **Exh. 22**.

   Testing method NJ.CR.LC2069-NJ.SP.15.EN was made effective on 6/26/2015 and refers to the revalidation of the analytical testing method, in which [redacted] is used as diluent for standard and sample preparations. Approximately seven batches have been manufactured using this method

(Exh. 22, pg. 3), which will be used to evaluate the effectiveness of CAPA 34615 for the revalidating the testing method. The analytical testing methods (revisions 12 to 15), change controls, PQRs (2012-2014), and the method validation for in process control, purity and related substance (Doc. Ref. NJ.CR.LC2069-NJ-SP.15.EN) were reviewed. The evaluation of testing results appeared adequate.

5. Items were discussed with management regarding HPLC system instability and testing method following the review of Deviation Report 41208 and corresponding supporting documentation. Deviation report 41208 **(Exh. 23)** for OOS result obtained during homogeneity study for validation batch 17TR68.NJ00006 (Assay spec. 97.0-102.0%, results 96.5%) attributed the root cause to HPLC system instability. Supporting records for this investigation were reviewed, which included a summary of injections peak area response factor **(Exh. 24)**, analytical data, method validation/transfer reports for CRLC4296, and CAPA 41279 **(Exh 25)**.

   CAPA 41279 was opened to further evaluate the event reported in deviation report 41208. During the analysis of 1-month stability sample at accelerated conditions, various injections of standard were conducted prior to sample analysis to evaluate the system. Approximately 26 injections of standard were required to equilibrate the system. The system provided good indication of stability in the last 6 injections (the peak area response factor of injections was evaluated). I discussed with Mr. Rodrigues and management that, if the system is properly maintained, and the testing method is adequate and validated, they should not be requiring such unusual number of injections prior to sample analysis. Management agreed with my observation.

   During the analysis of 3-month stability sample, the system was stable with 3 injections of standard. I discussed that I took into consideration they are evaluating the method via CAPA 41279, but they must confirm the instability of the system is due to the method, system, or column. They do not have dedicated columns and a different column was used during the analysis of samples (DR 41208, 1-month, and 3-month stability sample analysis).

   Mr. Rodrigues reported that, as noted in CAPA 41279, they will continue monitoring if the above incidents are singularities or if they are replicated during the analysis of commercial batches or stability samples. I said that, if the system instability continues, they must evaluate the analytical testing method (NJ.CR.LC4296.1.EN) and consider revalidation and/or changes. The method was validated in Hovione Portugal and transferred to the NJ site (validation and transfer reports were reviewed as mentioned above).

SAMPLES COLLECTED

No samples were collected during this inspection.

VOLUNTARY CORRECTIONS

During this inspection, it was observed the firm failed to assure the generation of analytical worksheets was controlled. During the closeout of the inspection, the firm presented change control records related to implemented changes to have adequate controls of the analytical worksheets. These included the creation of a new procedure SOP NJ.CO.SOP120.0.EN, Management of Controlled Copies Issued for Execution, approved on 12/14/2015. The new procedure instructs QA to print-out the fillable forms and distribute them. Additionally, the form must be embossed prior to its distribution to the QC department. An example of the log for controlled copies issued for execution, and the new embossed fillable method was reviewed and found adequate.

During this inspection, items discussed during the previous inspection were verified to be corrected. For example, the cleaning procedure, including record forms, was updated to clarify the use of water or acetone during cleaning; a functional verification was included in the equipment set up records of [redacted] to ensure that relevant functionalities are checked prior to equipment use.

ATTACHMENTS

1 Form 483 Hovione 12.16.2015
2 Form 482 Hovione 12.3.2015, 3 pages

EXHIBITS COLLECTED

1 NJ site overview presentation, 17 pages
2 Org Chart of Quality Unit at Hovione NJ, 1 page
3 Example of Method Analysis Request for 17TR68, 1 page
4 Doc Stream method print-out 17PA03, 2 pages
5 Empty fillable method form for [redacted] 17PA03, 32 pages
6 Empty fillable method form for [redacted] TR68, 44 pages
7 Completed worksheet for [redacted] lot 17PA03.NJ00052, 27 pages
8 Completed worksheet for [redacted] lot 16TR68030.NJ00007, 47 pages
9 SOP HQ.CCO.COP017.5.EN, 9 pages
10 SOP HQ.CCO.COP020.2.EN, 3 pages
11 Stability of intermediate assessment for [redacted], 4 pages
12 Hold time before using [redacted] intermediates, 3 pages
13 Retest period assesment for 16TR68020, 16TR68030 and 17TR68, 2 pages
14 Hold time before using [redacted] intermediates, 2 pages
15 correlation between the TR68M batches, 2 pages
16 Deviation Report 42747, 8 pages
17 Change Control ID7489, 3 pages
18 CAPA Report 22087, 2 pages
19 Deviation Report 13458, 5 pages
20 Deviation Report33953, 20 pages
21 CAPA Report 34615, 2 pages
22 Impurity at RRT 1.10 in 16PA03035, 3 pages
23 Deviation Report 41208, 9 pages

24 Summary injections for DR 41208, 2 pages
25 Deviation Report 41279, 2 pages

12/30/2015

X Maria Estrella

Maria Estrella
Investigator
Signed by: Maria Estrella -S

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10 Waterview Blvd. 3rd Floor Parsippany, NJ 07054 973-331-4900 Industry Information: www.fda.gov/oc/industry	12/3, 4, 7, 9, 10, 11, 16/2015
	FEI NUMBER 3006106736

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Marco A. Gil, Ph.D., General Manager

FIRM NAME	STREET ADDRESS
Hovione LLC	40 Lake Drive
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
East Windsor, NJ 08520	API 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) (WE) OBSERVED:

OBSERVATION 1

Procedures are not in writing and/or fully followed:

Specifically, details of laboratory analyses, such as sample and standard preparation, calculations, and results for APIs and/or intermediates [redacted] are captured on printed data sheets that can be printed multiple times by the analysts. There is no assurance that the generation of these documents is appropriately controlled.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	María Estrella	Maria E. Estrella, Investigator	12/16/2015

Hovione LLC
40 Lake Drive
East Windsor, NJ 08558
USA

NJ15.0478

18th December 2015

Food and Drug Administration
10 Waterview Blvd. 3rd Floor
Parsippany, NJ 07054
USA

To the attention of: Director of Compliance

Re: FDA Compliance Inspection on [redacted] on 3rd, 4th, 7th, 9th, 10th 11th and 16th of Decemeber, 2015

Dear Mr. Joseph F. McGinnis,

We refer to the inspection to our facility at New Jersey, USA, performed by your investigator Mrs. Maria E. Estrella on 3rd, 4th, 7th, 9th, 10th 11th and 16th of December, 2015.

This letter is our response to the one (1) observation that was raised during the inspection and was reported in the Form 483 issued.

OBSERVATION 1 - (Documentations Control)
"Procedures are not in writing and/or fully followed: Specifically, details of laboratory analyses, such as sample and standard preparation, calculations, and results for APIs and/or intermediates [redacted] and [redacted] are captured on printed data sheets that can be printed multiple times by the analysts. There is no assurance that the generation of these documents is appropriately controlled."

Response:
At Hovione, documentation related with the Quality System such as analytical testing methods are prepared and approved in the validated electronic documentation system called DocStream. All documents managed by DocStream have a unique reference number, version control, approval workflow, access control and electronic signatures. The system is 21 CFR Part 11 compliant. Members at Hovione have different access to the system depending on the access profile where the majority of the Hovione team members only have access to the latest approved document version.

As with all the other documents, analytical methods have their own unique method code with revision number automatically updated upon being revised. Whenever analysts need to perform an analytical testing, two procedures may be followed depending on the type of method defined:

a) Traditional analytical method – analysts assess the method through the view panel of DocStream and perform the analysis according to what is described in the method. All raw data is recorded in the analyst and/or equipment notebook;

b) Fill in analytical method form – in this case, the method is prepared in a fill-in format for analysts to fill out along the analysis. The analysts will have to print the approved fill-in method from DocStream to document the execution of the analysis.

Procedures are in place to instruct the printing of this type of method ensuring only copies directly printed from DocStream, with the trail of when it is printed, are used for execution. Nonetheless, the system allows multiple copies of the same method to be printed and does not track the number of printed copies.

Even though there is no evidence of analysts printing multiple copies of the fill-in methods for execution, Hovione acknowledged that the control in place should be enhanced during the gap analysis performed to assure data integrity. A plan is in place to enhance the control of the print-out, but it has not been implemented at the time when the inspection occurred leading to the observation.

Upon receiving the concern from the inspector further confirming the criticality of improving the control system, Hovione recognizes the control in place has to be enhanced promptly.

To address this observation, the following correction, corrective and preventive actions were identified and were immediately implemented.

Correction:
The plan to further improve the control system for analytical fill-in methods was approved for implementation through the change control request with reference ID.7492 (Annex1) on 11.Dec.2015.

Per the change control request, the new procedure, Management of Controlled Copies Issued for execution with reference NJ.CO.SOP120.0.EN (Annex 2), was created and set as effective for usage on 14.Dec.2015. This procedure defines the control system for all controlled documents where all documents that are to be populated with data are printed by Quality Assurance (QA), who will control and track the number of copies through the record form with reference NJ.QSD.QARF060 (Annex 3). All print-outs must be embossed by QA with Hovione logo to be considered a true, controlled copy to be used for execution (Exhibit 1). The embossing machine has an ON-OFF lock to control access, and only QA has the key to operate. Upon receipt of the embossed documents, the requester or the recipient must acknowledge the reception by signing and dating NJ.QSD.QARF060 (Annex 3). In order to ensure all printed copies are reconciled, the reviewer will need to verify the number of issued copies. For process-related documents, the verification will be documented on NJ.QSD.QARF009 (Annex 4). For analytical fill-in methods, the verification will be documented in NJ.QSD.QCRF079 (Annex 5). For analytical method validation fill-in protocols and equipment validation protocols, the verification will be documented in the protocols by the reviewer upon completion of the review.

Training was provided to all relevant Departments on the above mentioned procedure (Annex 2) on 14.Dec.2015 and the procedure was implemented accordingly on the same day. Annex 3 is an example of the executed NJ.QSD.QARF060 to demonstrate the execution of the above procedure.

Hovione

18th December 2015

Corrective Action:
The control is extended to all analytical fill-in methods based on the procedure, NJ.CO.SOP120.0.EN (Annex 2). This corrective action is considered concluded.

Preventive Action:
The control is extended to documents other than analytical fill-in methods to be printed for populating data to support GMP activities on site. The control procedure is stated as above and documented in NJ.CO.SOP120.0.EN (Annex 2). This preventtive action is considered concluded.

The above actions were concluded before the end of the inspection and were presented with evidences of the execution to the inspector, which were found to be acceptable.

We trust this response addresses adequately the observation 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.

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

Marco Gil
General Manager
Tel: +1 609 918 2456
Cell: +1 609 731 4740
mgil@hovione.com

cc: Maria E. Estrella – Investigator (e-mail)
Enclosures

List of enclosures:

Annex ref.	Description	Page
Annex 1	Change Control Request (reference ID.7492)	4 – 10
Annex 2	NJ.CO.SOP120.0.EN – Management of Controlled Copies Issued for Execultion with reference NJ.CO.SOP120.0.EN	11 – 13
Annex 3	NJ.QSD.QARF060.1.EN – Controlled Copies Issued for Execution (Executed example)	14 – 15
Annex 4	NJ.QSD.QARF009.3.EN – Certificate of Analysis Approval / Batch Release	16
Exhibit 1	Hovione Logo Embossed Sample	19

Annex 1: Change Control Request (ID#7492)

Control of Fill-In Methods

Site	ID	Date	Level	Classification
NJ	7492	2015.12.10 09:27:35 PM	Minor	Analytical Methods

Issued by	Required by	Project	Workflow State
Deborah Green	2016.02.15	N/A	Under Implementation

Issuing Area
Hovione New Jersey-NJ .NJ

Change Control Description

Objective

The objective of this change request is to change the current procedure for printing controlled copies of fill-in analytical methods.

Rationale

Currently, controlled fill-in methods are printed by Quality Control (QC) Analysts through the validated document system, Docstream. It is proposed to change this printing responsibility from QC Analysts to the Quality Assurance department (QA) in order to further enhance the control of the analytical fill-in methods.

Even though the current procedure requires QC Analysts to print directly from Docstream, where the date and time of the print-out is displayed on the printed document, the number of copies printed is not captured. Therefore, in order to ensure the number of printed copies can be traced and that only copies generated directly from Docstream are used, it is proposed to have QA performing the printouts upon request from the QC Analysts.

This proposed procedure aligns with the current procedure being used by QA to control printing and distribution of batch production records. Upon printing the controlled fill-in method from Docstream, QA will then emboss the controlled copy with the Hovione logo in the upper right corner of each sheet using the embossing machine to further evidence that the printed copy is an original, official copy to be used for execution. Since the embossing machine is locked and can only be accessed by QA, the control of the issuance of the fill-in analytical methods from the system is assured.

Distribution of the controlled embossed copies will be recorded in the logbook, in which the sample-specific LIMS number and the associated printed controlled copies are documented. Both the issuer and the recipient of the distributed documents will have to sign and date in the logbook.

Upon review of the analytical package for release, the Peer Reviewer will need to verify the number of copies issued and ensure that all issued copies are incorporated into the analytical package to assure integrity.

With the implementation of the above proposed control system, the control of the integrity of the analytical data can further be enhanced.

To have the system implemented, the following tasks will have to be performed:

1. Revise the instructions on all fill-in methods to clearly iterate the proper procedure for printing/issuing controlled copies for execution.
2. Revise the Peer Review Checklist QCRF079.0 to add an item for verification that all the copies

issued by QA are included in the analytical package.

3. Create record form to control the issued copies.
4. Create a procedure to document the specific controlling system for paper based documents at Hovione NJ.
5. Provide training to QC and QA personnel on the new procedure.
6. Evaluate the implementation of the proposal.

Impact Analysis

There is no quality impact of the proposed change as the proposed could only further enhance the controls in place for analytical fill-in methods. Therefore, the change control is considered as minor.

Items under assessment

Item	Due date	Comment	State
Product Quality Request by: Deborah Green Assessment to be done by: Jenny Fong (NJ) Concluded	2015.12.11		• Send Message

Messages

Product Quality

From: **Jenny Fong (NJ)** - Date: 2015.12.10 23:51:50- ID: 103990.0-Active

Subject: Product Quality

I agree with the proposed changes as with the proposed procedures, the control of the analytical fill-in methods could be further enhanced to ensure data integrity.

Analytical Methods and Specifications Request by: Deborah Green Assessment to be done by: Nuno Rodrigues Concluded	2015.12.11		• Send Message

Digital Signature on record content is **Valid** — **Audit Trail**

Audit id	Audit Date	User name	Action	Workflow Task	Resulting State	e-Sig
10510423	2015.12.11 00:35:06	Jenny Fong (NJ) Messages	**Standard approval** form: Send to next state	Approve and implement	Under Implementation	Valid
			With the assessment performed on the proposal with all the appropriate tasks defined to ensure successful implementation of the proposal, the change request is approved for implementation.			
10510422	2015.12.11 00:33:15	Deborah Green Messages	**Submit plan for approval** form: Send to next	Minor Impact - Send for standard approval	Pending approval	standard Valid

			state			
10510421	2015.12.11 00:33:14	Deborah Green Messages	**Change record** form: Edit Form - Update level			Valid
10510409	2015.12.11 00:24:41	Jenny Fong (NJ) Messages	**Standard approval** form: Send to next state	Send back for further planning	Under Assessment	Valid
			The proposed tasks should be added for implementation.			
10510386	2015.12.11 00:17:16	Deborah Green Messages	**Submit plan for approval** form: Send to next state	Minor Impact - Send for standard approval	Pending standard approval	Valid
10510385	2015.12.11 00:17:15	Deborah Green Messages	**Change record** form: Edit Form - Update level			Valid
10510071	2015.12.10 21:29:00	Deborah Green Messages	**Issue change request** form: Send to next state	Issue change control	Under Assessment	Valid
10510070	2015.12.10 21:27:35	Deborah Green Messages	**New record** form: New Change Request			Valid

All Messages for this Change Control

Messages

Product Quality

From: **Jenny Fong (NJ)** - Date: 2015.12.10 23:51:50- ID: 103990.0-Active

Subject: Product Quality

I agree with the proposed changes as with the proposed procedures, the control of the analytical fill-in methods could be further enhanced to ensure data integrity.

Control on Batch Production Records, Unbound Record Forms and Fill-in Protocols

From: **Jenny Fong (NJ)** - Date: 2015.12.14 23:11:26- ID: 104087.0-Active

Subject: Control on Batch Production Records, Unbound Record Forms and Fill-in Protocols

In addition to implementing additional control on analytical fill-in methods, the same control mechanism is implemented for all process related GMP documents (e.g. Batch Production Records, unbound record forms used to support the process) and fill-in protocols used for equipment qualification and method validation. The control in place is detailed in the newly created Site Operating Procedure. N1.QSD.SOP120 that is approved and set as effective as of 14.Dec.2015. To support the

implementation of NJ.CO.SOP120.0.EN, NJ.QSD.QARF009.2.EN, NJ.QSD.QARF060.0.EN and NJ.QSD.QCRF079.0.EN are revised to NJ.QSD.QARF009.3.EN, NJ.QSD.QARF060.1.EN and NJ.QSD.QCRF079.1.EN. There is no impact of the above revisions and the control system in place aligned with the approved proposal for analytical fill-in methods.

Tasks

Task: Revise the instructions on all fill-in methods to clearly iterate the proper procedure for printing/issuing controlled copies for execution.

From: **Deborah Green** - Date: 2015.12.11 00:30:48- ID: 103991.0

To: **Deborah Green,**

Subject: Revise the instructions on all fill-in methods to clearly iterate the proper procedure for printing/issuing controlled copies for execution.

Revise the instructions on all fill-in methods to clearly iterate the proper procedure for printing/issuing controlled copies for execution.

Audit:

Mark as read and set as ongoing by Deborah Green on 2015.12.11 01:05:05

RE: Revise the instructions on all fill-in methods to clearly iterate the proper procedure for printing/issuing controlled copies for execution.

Reply From: **Deborah Green** - Date: 2015.12.16 17:28:27- ID: 104282.0-Active

To: **Deborah Green,**

Subject: RE: Revise the instructions on all fill-in methods to clearly iterate the proper procedure for printing/issuing controlled copies for execution.

Note that in the interim, for those existing fill-in methods that have not yet been revised, when issuing a controlled copy, any references in the instructions related to printing will be crossed, signed/date by QA, and a note will be included on the first page to state: "Per PdA 7492, refer to CO.SOP120 for the procedure related to printing of this document." which will also be signed/dated by QA.

Task: Revise the Peer Review Checklist QCRF079.0 to add an item for verification that all the copies issued by QA are included in the analytical package.

From: **Deborah Green** - Date: 2015.12.11 00:30:48- ID: 103992.0

To: **Deborah Green,**

Subject: Revise the Peer Review Checklist QCRF079.0 to add an item for verification that all the copies issued by QA are included in the analytical package.

Revise the Peer Review Checklist QCRF079.0 to add an item for verification that all the copies issued by QA are included in the analytical package.

Audit:

Mark as read and set as ongoing by Deborah Green on 2015.12.11 01:03:08

Mark as completed by Deborah Green on 2015.12.14 23:13:47

QCRF079.1 was set effective at the NJ site on 2015.12.14.

RE: Revise the Peer Review Checklist QCRF079.0 to add an item for

verification that all the copies issued by QA are included in the analytical package.

Reply From: **Deborah Green** - Date: 2015.12.15 01:29:32- ID: 104115.0-Active

To: **Deborah Green,**

Subject: RE: Revise the Peer Review Checklist QCRF079.0 to add an item for verification that all the copies issued by QA are included in the analytical package.

Also - QARF009.2 was revised to rev 3 to add item for verification that all the copies issued by QA are included in the analytical package.

QCRF009.3 was set effective at the NJ site on 2015.12.14.

RE: Revise the Peer Review Checklist QCRF079.0 to add an item for verification that all the copies issued by QA are included in the analytical package.

Reply From: **Deborah Green** - Date: 2015.12.15 01:32:02- ID: 104116.0-Active

To: **Deborah Green,**

Subject: RE: Revise the Peer Review Checklist QCRF079.0 to add an item for verification that all the copies issued by QA are included in the analytical package.

There is a typographical error on message 104115.0. Last line should read:

QARF009.3 was set effective at the NJ site on 2015.12.14.

Task: Create record form to control the issued copies.

From: **Deborah Green** - Date: 2015.12.11 00:30:49- ID: 103993.0

To: **Deborah Green,**

Subject: Create record form to control the issued copies.

Create record form to control the issued copies.

Audit:

Mark as read and set as ongoing by Deborah Green on 2015.12.11 01:04:07

Mark as completed by Deborah Green on 2015.12.15 01:20:07

QARF060.1 is effective.

RE: Create record form to control the issued copies.

Reply From: **Deborah Green** - Date: 2015.12.15 01:19:05- ID: 104098.0-Active

To: **Deborah Green,**

Subject: RE: Create record form to control the issued copies.

No new record form was created. QARF060.0 was revised to rev 1 to accommodate issue of all controlled documents, therefore this can be considered complete.

Task: Create a procedure to document the specific controlling system for paper based documents at Hovione NJ.

From: **Deborah Green** - Date: 2015.12.11 00:30:49- ID: 103994.0

To: **Deborah Green,**

Subject: Create a procedure to document the specific controlling system for paper based documents at Hovione NJ.

Create a procedure to document the specific controlling system for paper based documents at Hovione NJ.

Audit:
Mark as read and set as ongoing by Deborah Green on 2015.12.11 01:04:28

RE: Create a procedure to document the specific controlling system for paper based documents at Hovione NJ.

Reply From: **Deborah Green** - Date: 2015.12.15 01:23:41- ID: 104104.0-Active

To: **Deborah Green,**

Subject: RE: Create a procedure to document the specific controlling system for paper based documents at Hovione NJ.

NJ.CO.SOP120 was created to document the procedure for Management of Controlled Copies. Procedure is set effective 2015.12.14.

Task: Provide training to QC and QA personnel on the new procedure.

From: **Deborah Green** - Date: 2015.12.11 00:30:50- ID: 103995.0

To: **Jenny Fong (NJ),**

Subject: Provide training to QC and QA personnel on the new procedure.

Provide training to QC and QA personnel on the new procedure.

Audit:
Mark as read and set as ongoing by Jenny Fong (NJ) on 2015.12.16 16:12:35
Mark as completed by Jenny Fong (NJ) on 2015.12.16 16:22:31
Training was provided on 2015.12.14, refer to training session #31159.

RE: Provide training to QC and QA personnel on the new procedure.

Reply From: **Jenny Fong (NJ)** - Date: 2015.12.16 16:21:21- ID: 104277.0-Active

To: **Deborah Green, Jenny Fong (NJ),**

Subject: RE: Provide training to QC and QA personnel on the new procedure.

Based on message#104087.0, the proposal will cover documents impacting all departments involved in GMP activities, training was provided to all team members from Production, Analytical Development, Quality Assurance and Quality Control Departments.

Refer to Session #31159 for the training provided.

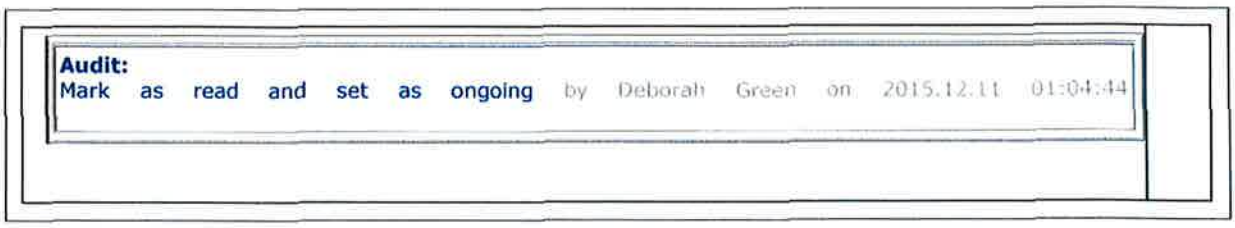
Task: Evaluate the implementation of the proposal.

From: **Deborah Green** - Date: 2015.12.11 00:32:10- ID: 103996.0

To: **Deborah Green,**

Subject: Evaluate the implementation of the proposal.

Evaluate the implementation of the proposal.


Audit:
Mark as read and set as ongoing by Deborah Green on 2015.12.11 01:04:44

Annex 2: NJ.CO.SOP120.0.EN – Management of Controlled Copies Issued for Execution

Hovione

Standard Operating Procedure - CO	
Ref.: NJ.CO.SOP120.0.EN	
Management of Controlled Copies Issued for Execution	Page: 1 / 3
Effective adoption site: NJ Marco Gil 2015.12.14 23:33:21	

Prepared	Quality Approved	Content Approved
Deborah Green 2015.12.14 23:07:38	Jenny Fong (NJ) 2015.12.14 23:13:04	Marco Gil 2015.12.14 23:17:27

1. **Purpose**

Define the requirements for controlled documents print-outs.

2. **Scope**

This procedure applies to any document printed from DocStream that is used to record GMP related data pertaining any operation or analysis. Embossed print-outs of these documents are considered controlled copies.

3. **Introduction**

Hovione uses DocStream to manage and control all documents. The DocSteam system is able to track the number of electronically distributed copies, but the physical number of printouts is not tracked. The control of documents is in accordance with the procedures in place ensuring only the designated responsible department and personnel maintain the integrity of the procedures.

For documents such as Corporate Operating Procedures (COP), Standard Operating Procedures (SOP) and Internal Operating Procedures (IOP) that are used as references, all distributed controlled copies are tracked in the system and managed by Quality Assurance (QA).

For documents created for the purpose of populating data (e.g. batch production records [BPR], fill-in methods and record forms not bound as logbooks), as the system is not able to track the number of copies printed out, QA must track and record the number of copies issued. The number of issued copies is verified by the reviewer to ensure that all copies are reconciled and included in the batch or data package.

4. **Responsibilities**

SUBJECT	RESPONSIBILITY
To request controlled copies of procedures to be used for contingency purposes or in user area that does not have access to computers	IO (Process Engineering), QC (Quality Control), Analytical Development (AD)
To request controlled copies of documents to be populated (e.g. BPR, Fill-in methods/protocols, unbound record forms, etc.) to QA	IO, QC, AD
To issue controlled copies of the requested documents either through the issuance of logbook or individual copies for a specific purpose/location	QA
To verify the number of copies issued to ensure all issued copies are reconciled	QC for analytical fill-in methods and method validation reports; QA for all GMP process related documents

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Printed on 2015.12.14 23:34

5. Procedure

In order to ensure data integrity of documents used to record data of operations/analysis, the number of copies issued for controlled documents must be controlled by an independent area, namely QA.

There are three types of documents that may be printed as controlled copies:

- **Procedures** (COP, SOP, IOP)
- **Logbooks** that contain a set of record forms that are used to record data by different areas
- **BPRs, unbound Record Forms and Fill-in methods/protocols to be populated**

5.1. Procedures (COPs, SOPs, IOPs)

Upon being set as effective, all COP, SOP and IOP are distributed and printed by QA to be used for contingency purposes in the event the DocStream system is temporarily down or the usage of the procedure is needed in an area without access to a computer (e.g. Manufacturing areas). For these copies, upon revision, the copies of the previous revision are immediately substituted by QA upon the notification that a new document or a new revision has been set effective. The location where these controlled copies are distributed is tracked the in DocStream system.

The notification made to QA on the creation of a new document or new revision of a previously distributed document is ensured by the approver of the document. The approver is responsible to activate the request for the necessary distributed controlled copy(ies) in Docstream. QA is responsible to print and record the location of the controlled copy(ies) in DocStream.

5.2. Logbooks

Certain record forms, which are used for multiple projects or for continuous usage (e.g. internal verification of weigh scales, equipment usage and cleaning, etc.), are bound together as a logbook. Record forms to be bound as logbooks contain a disposition line in the footer indicating that copies of the record form are part of a logbook. These logbooks are issued by QA upon the request of the user area when a new record form or a new revision is approved and when the previous logbook is about to be used up. Upon completion of the logbooks, it is also QA responsibility to archive and store them per the minimum storage period defined in the related Hovione procedure [1].

5.3. BPRs, unbound Record Forms, Fill-in Methods and Protocols

Documents that are to be populated are printed by QA, who will control and track the number of copies through NJ.QSD.QARF060. All such print-outs must be embossed by QA with the Hovione logo to be considered a true, controlled copy to be used for execution. The embossing machine has an ON-OFF lock to control access, and only QA has the key to operate. Upon receipt of the embossed documents, the requester or the recipient (IO, QC or AD) must acknowledge the reception by signing and dating NJ.QSD.QARF060. In order to ensure all printed copies are reconciled and included in the appropriate data package, the reviewer will need to verify the number of issued copies. For process-related documents, the verification will be documented on NJ.QSD.QARF009. For analytical fill-in methods, the verification will be documented in NJ.QSD.QCRF079. For analytical method validation fill-in protocols and equipment validation protocols, the verification will be documented in the protocols by the reviewer upon completion of the review.

6. Records

The records of issuance and verification of controlled copies are kept in:

1 - DocStream system – for COPs, SOPs and IOPs;
2 - QSD.QARF009 – Certificate of Analysis Approval / Batch Release;
3 - QSD.QARF046 – Logbook Record;
4 - QSD.QARF060 – Controlled Copies Issued for Execution;
5 - QSD.QCRF079 – Peer Review Checklist.

7. References

[1] ICH Q7 – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
[2] CCO.COP001 – Document Control and Procedure Format

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Annex 3: NJ.QSD.QARF060.1.EN – Controlled Copies Issued for Execution (Executed example)

Hovione

Controlled Copies Issued for Execution

Ref.: CO.SOP120

PROJECT CODE: [redacted] ☐ N/AP

Quality Assurance and Recipient must sign and date below as indicated.

Batch / Sample or Sequential Nr.	Document Reference CC.TTTSSS_PP.R*	Quality Assurance: Copies issued – Date	What was issued? – Full copy	What was issued? – Partial: Specify page number(s) **	Comment – Reference Nr.	Document embossed – Yes ☒	Quality Assurance: Page count and sequence verified – Sign/Date	Recipient: Page count and sequence verified – Sign/Date	Reviewer – Sign/Date
NJ00008	NJ.PD.BPR.[redacted]	14-DEC2015	☒	☐	☒ N/AP	☒	BZP 14-DEC-2015	ASD 14.Dec.2015	
			☐	☐	☐ N/AP	☐			
			☐	☐	☐ N/AP	☐			
NJ00009	NJ.PD.BPR.[redacted]	14.Dec.2015	☒	☐	☒ N/AP	☒	BZP 14.Dec.2015	ASD 14.Dec.2015	
			☐	☐	☐ N/AP	☐			
			☐	☐	☐ N/AP	☐			
NJ00008	NJ.PD.CKL.[redacted]	12-Dec-2015	☒	☐	☒ N/AP	☒	BZP 14-DEC2015	ASD 14.Dec.2015	
			☐	☐	☐ N/AP	☐			
			☐	☐	☐ N/AP	☐			
NJ00009	NJ.PD.CKL.[redacted]	14-Dec-2015	☒	☐	☒ N/AP	☒	BZP 14-Dec-2015	ASD 14.Dec.2015	
			☐	☐	☐ N/AP	☐			
			☐	☐	☐ N/AP	☐			
NJ00008	NJ.QSD.JORF1193	14-Dec.2015	☒	☐	☒ N/AP	☒	BZP 14-Dec-2015	ASD 14.Dec.2015	
			☐	☐	☐ N/AP	☐			
			☐	☐	☐ N/AP	☐			
NJ00009	NJ.QSD.JORF1193	14-Dec-2015	☒	☐	☒ N/AP	☒	BZP 14-Dec-2015	ASD 14.Dec.2015	
			☐	☐	☐ N/AP	☐			
			☐	☐	☐ N/AP	☐			

* CC = Document class TTT = Document type SSS = Sequential nr. PP = Process nr. (if applicable) R = Revision

** If any original pages were destroyed, please explain in comments on reverse. Note that destruction of pages from documents that have already begun execution in the Manufacturing area is not permitted.

PAGE 1

Ref.: NJ.QSD.QARF060.1.EN Approved: Jenny Fong (NJ) 2015.12.14 23:18:48 CONFIDENTIAL Page: 1 / 2

Hovione

Controlled Copies Issued for Execution

Ref.: CO.SOP120

Comments

Ref. Nr.	Comment

PAGE 2

Ref.: NJ.QSD.QARF060.1.EN

Approved: Jenny Fong (NJ) 2015.12.14 23:18:48 COMPANY

Page: 2 / 2

Annex 4: NJ.QSD.QARF009.3.EN – Certificate of Analysis Approval / Batch Release

Non controlled

Hovione

Quality System Documentation - QSD	
Ref.: NJ.QSD.QARF009.3.EN	
Certificate of Analysis Approval / Batch Release	**Page:** 1 / 1
Effective adoption site: NJ Jenny Fong (NJ) 2015.12.14 23:16:23	
Prepared Deborah Green 2015.12.14 17:20:21	**Content Approved** Jenny Fong (NJ) 2015.12.14 23:16:23

Ref. CCO.COP022, CCO.COP013

PRODUCT CODE	PRODUCT BATCH NO. NJ. ___ ___ ___ ___ ___

MANUFACTURING — This section to be completed by the Quality Assurance Unit [QAU].

1.	Have the batch production records for all steps been reviewed and signed?	Yes ☐	No ☐	N/AP ☐
1.1	Has the number of process documentation copies issued been verified?	Yes ☐	No ☐	N/AP ☐
2.	Batch production records included in attachment:			
2.1	Printouts of all process parameters during operation.	Yes ☐	No ☐	N/AP ☐
2.2	Packing room T and RH trending.	Yes ☐	No ☐	N/AP ☐
3.	Did any deviations occur?	Yes ☐	No ☐	N/AP ☐
3.1.	Have all deviations (non-critical and critical) been investigated and the necessary corrective actions defined?	Yes ☐	No ☐	N/AP ☐

Signature (Initials:___):_____ Date:___/___/___

QUALITY CONTROL — This section to be completed by the QAU.

4.	Have all the raw materials for the final product been reviewed and approved in SAP?	Yes ☐	No ☐	N/AP ☐
5.	Were there any analytical deviations related to intermediate products or the final product release testing?	Yes ☐	No ☐	N/AP ☐
5.1	Were all analytical deviations (non-critical and critical) investigated and corrective actions defined?	Yes ☐	No ☐	N/AP ☐
6.	Was there any additional analytical testing required by the client?	Yes ☐	No ☐	N/AP ☐
7.	Did client request copies of raw data (including logbooks)?	Yes ☐	No ☐	N/AP ☐
7.1	If yes, have the copies been prepared?	Yes ☐	No ☐	N/AP ☐

NOTES: (indicate all deviations requiring client approval)

Signature (Initials:___):_____ Date:___/___/___

COMMENTS — This section to be completed by the QAU.

_____

_____

_____

FINAL ASSESSMENT — This section to be completed by the QAU.

8.	Does batch Certificate of Analysis (CofA) conform to the product specification? (Initials:___):_____ Date:___/___/___	Yes ☐	No ☐	N/AP ☐
8.1	Is batch CofA approved and signed by QA? (Initials:___):_____ Date:___/___/___	Yes ☐	No ☐	N/AP ☐
8.2	Is batch CofA approval documented in SAP? (Initials:___):_____ Date:___/___/___	Yes ☐	No ☐	N/AP ☐
8.3	Is annex attached (flowchart for Intermediates and Final product sequence, including any deviations)?	Yes ☐	No ☐	N/AP ☐
8.4	**For commercial products:** Has the NavStream data been checked?	Yes ☐	No ☐	N/AP ☐

Upon completion this form is filed in the Batch Production Record with the Certificate of Analysis.

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Note: Revision made to support the change is highlighted

Annex 5: NJ.QSD.QCRF079.1.EN – Peer Review Checklist

Peer Review Checklist

Ref.: QC.IOP024

General verifications		YES	NO	N/AP
1.	The analyst/chemist has been qualified in the analytical technique associated with the work being reviewed.			
2.	All controlled fill-in methods copies issued by QA are included in the analytical package.			
3.	Documentation in the analytical data package (chromatograms, IR spectrums, UV printouts, particle size distribution reports and printouts of outsourced lab reports) has been signed and dated (electronic or hand written signature).			
4.	All analytical data package documentation has the correct Hovione date and time format.			
5.	Operational conditions used were in accordance with the current analytical method revision, and if no unauthorized changes to the method were done during testing.			

Analytical documentation verifications		YES	NO	N/AP
6.	'Start' has been entered on the first page where the analysis is being documented.			
7.	Header - 'Project and type of test' entered in the laboratory notebook (if applicable).			
8.	Stamp or the following information requisition number, product code and product name was recorded in the notebook and is filled out correctly.			
9.	Current specification reference is recorded, if applicable.			
10.	Current method reference and revision are recorded/present and in alignment with the specification in force.			
11.	Instrument/equipment (e.g. micro pipettes) information and calibration due date are recorded and valid.			
12.	Equipment maintenance and/or preventive maintenance were valid at the time the analysis was carried out.			
13.	Solvent, reagent and standard information and expiration date recorded.			
14.	Reference standards used were within retest date established in the correspondent Certificate of Analysis.			
15.	Standard/Retention time markers preparation, if available, and sample preparation recorded.			
16.	Standard/Retention time markers and Sample solution expiration date recorded.			
17.	HPLC/GC Column characteristics (details recorded in QSD.QC.RF005) are accordingly to the method and dully recorded in HPLC/GC column usage record form (refer to QSD.QC.RF024).			
18.	Test solution, volumetric solution, and/or mobile phase preparation recorded with the respective expiration date			
19.	Correct glassware was used? E.g.: Class A glassware, pipettes, and calibrated micro pipettes.			
20.	Appropriate printouts are attached, and analyst has signed and dated across each printout to the document page to which they are attached.			
21.	Date and time are correct.			
22.	All printouts are labeled with Sample ID and/or preparation number.			
23.	Daily verifications of equipment were performed (e.g weigh scales), if applicable.			
24.	All weights are within +/-10% of specified weight unless otherwise specified in the individual method.			
25.	Was the time (e.g.: start and end time) recorded if method requires a time period for testing, standard preparation, or pre-testing preparation? **Examples:** LOD oven drying times, ROI furnace ignition time, sample allotted time for reaction completion, etc.			

Ref.: NJ.QSD.QCRF079.2.EN **Approved:** Nuno Rodrigues 2015.12.15 20:44:30
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Note: Revision made to support the change is highlighted.

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Peer Review Checklist

Ref.: QC.IOP024

	Analytical documentation verifications	YES	NO	N/AP
26.	All chemicals and solvents used have been cross referenced to Brand/Part Number, Lot No., and expiration date.			
27.	Calculations are accurate.			
28.	At least one example of each different calculation used is recorded, if not already available from the validated instrument software in use. (Example: RSD, Mean, SD, % Difference, etc.)			
29.	All errors are crossed out with a single line and are still legible and are duly justified when the correction is not obvious.			
30.	All corrections have at least the initial of the person who corrected the error, the date when the correction was made and the justification for the correction adjacent/cross referenced to the error.			
31.	All words or letters that are not legible or clear are considered an error. The analyst has rewritten the word or letter after crossing out the illegible one and has provided an explanation such as 'rewritten for clarity'.			
32.	All test results are recorded with the correct significant figures as per the specification, batch production record, protocol or method.			
33.	The criteria for the test has been written along with 'Pass or Fail' next to each result, if associated with a specification or protocol acceptance criteria.			
34.	If documentation of the testing extends beyond one page, each page makes reference to the preceding and proceeding pages. Note: For notebooks, the first page of the documented testing should begin with the word 'start', and the last page should conclude with the word 'end'.			
35.	If more than three unused lines remain at the bottom of a page, the unused portion of the page is crossed out, and the phrase 'N/AP' is written above the diagonal line.			
36.	Analyst's signature is present in the reserved spaces of each page along with the date the signature was made.			
37.	For electronic systems, the data package being provided for one analysis is in accordance with the electronic records generated. Any eventual discrepancies were duly justified in the system audit trail or in the notebook/fill-in method/ fill-in protocol.			
38.	If all records are in accordance with section 5.1.3, the Peer Reviewer has signed and dated in the reserved spaces to indicate completion of the peer review task.			

Comments/Observations

Reviewed by: _____ _____

Signature *Date*

Upon completion this record form is retained with the analytical documentation to which is it associated.

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18th December 2015

EXHIBIT 1