DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave. Bldg. 51, Rm. 4225 Silver Spring, MD 20993 (301) 796-3334. Fax: (301) 847-8738 Industry Information: www.fda.gov/oc/industry	5/16/2016 - 5/20/2016
	FEI NUMBER 3008058822

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Paul C. Downing, Ph.D. General Manager

FIRM NAME	STREET ADDRESS
Hovione Limited	Loughbeg
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Ringaskiddy, Co. Cork, Ireland	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.

The observations noted in this Form FDA 483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

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

Quality

OBSERVATION 1:

There is a failure to thoroughly review deviations and the associated corrective or preventive actions. Specifically, some of your corrective and preventive actions were not adequate. For example,

A. Your firm received a customer complaint on 29Apr2015 about the open aluminum seal for packaged SDD product batch HE00043. While the investigation carried out under deviation 40023 did not identify definitive root cause of the failure, several corrective actions were implemented such as better protection of the aluminum bag to prevent possible dusk contamination and double heat seals to be used for the packaging process. However, the double seal process was implemented only in the master production record for SDD product. Such corrective action was not extended to other SDD products that used the same packaging material and process, such as SDD product At the time of this inspection, the packaging process for SDD product still requires only single seal on the aluminum bag.

B. During visual inspection of sieve on DISP-10-20-1000 equipment at the end of manufacturing process for SDD product batch HE00006, a stainless steel piece and two pieces of thread were found on the sieve. An investigation was conducted under deviation 40226 and the sources of these foreign objects were identified to be related to sampling thief and personnel gowning material. It was suspected that these foreign objects had fallen into the SDD product during sampling process. While corrective actions were taken to use disposable sampling thief and revising the sampling instruction, the investigation failed to assess the adequacy on the quality of the gowning materials used in the production room.

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		Liming Zhang, Investigator	05/20/2016

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C. There is no evidence established that the SDD product batch HE00060 manufactured on 15Feb2016 with partially opened valve under cyclone could still meet the quality specification at the end of its shelf life. During batch HE00060 manufacturing, the spray dryer was shut down by operator in a controlled manner after approximately 2 hours into the operation due to an observation that the expected amount of SDD product was not discharged into the IBC. The cause of this incident was identified to be the valve XCV-10-07-6201 under the cyclone being not fully open during operation which resulted in built up of SDD powder in cyclone. The investigation under deviation 46297 discovered that the valve position had been adjusted incorrectly by the shift electrician prior to the spray drying operation. There was about 7.66 kg of SDD product accumulated in cyclone due to this incident. The accumulated product was recovered, segregated, and was not considered suitable for release as they were not produced through an intended manufacturing process. The investigation concluded that the SDD product discharged into the IBC during the initial 2 hours of spray drying was not considered to be impacted by this event and therefore the collected product in IBC was packaged and released. However, the deviation investigation failed to take into consideration of the fact that the SDD product collected into IBC during the first two hours of operation was also subjected to the unintended manufacturing process in that the powder could have also been accumulated in the cyclone for a certain period of time before being discharged into the IBC due to the partially opened valve.

Facility and Equipment

OBSERVATION 2:

Your firm's production equipment is not verified to operate in the qualified range. Specifically,

The Polystar DSM400 bag sealer with equipment ID HSM-35-10-1000 is used as part of the spray dried dispersion (SDD) product packaging process in building 10 by providing seal to the aluminum bags that are used as secondary container closure system for the SDD products such as SDD and SDD. While the sealing operation was qualified at the temperature range of 130°C to 135°C, the following deficiencies are noted,

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A. The heating temperature was not verified. There is a lack of assurance that the actual heating temperature can be achieved and maintained consistently with the same temperature setting on the machine.

B. The height of sealing position on the aluminum bag was not defined. There is no assurance that the sealing position during batch production was identical to that of the sealing process qualification study.

C. During SDD product batch production, the actual sealing machine temperature was not documented. There is no evidence that the sealing machine temperature was set within the qualified temperature range.

Production

OBSERVATION 3:

Your firm's batch production records did not include the actual values from some of the operating parameters for the SDD product manufacture operations. Specifically,

A. The instruction in step 11.3 and step 11.4 of the master batch record HE.PRD. 2.EN states "all test samples for should be prepared in conditions of less than 10% relative humidity. Ensure humidity in glove bag is below this level during sample preparation." However, there is no record of the actual humidity value achieved at the time of sample preparation. In addition, the identification of the glove bag and the humidity probe were not recorded in the batch production record. Therefore, there is no evidence that samples were actually prepared in the required humidity condition instructed in the batch production record. Similar deficiency was also seen in the batch production records for SDD product.

B. The instruction in step 11.2.7 of the same master batch record as item A above states "Seal the AL bag according with QSD.IF493, expel the air from the bag before sealing – sealing machine temperature to be 130-135°C." The actual sealing temperature was never recorded in the batch production record for SDD products. Similar deficiency was also observed in the batch production records for SDD product.

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Laboratory Control

OBSERVATION 4:

The system suitability of the test method is not verified at the actual condition of use. Specifically,

The test results of assay and related substance for SDD product batch HE00004 and HE00005 was generated without system suitability being established for the analysis sequence LC4606_2015_05_15_System. The sequence was originally started with system suitability test, but the UPLC system stopped abruptly prior to the test sample analysis. According to your QC lab senior analyst TS, the UPLC system was interrupted and the mobile phase flow was stopped for about 3 minutes. However, the same UPLC analysis sequence was allowed to resume by including only one additional standard to evaluate the system drift. The system suitability was not re-verified. Therefore, the samples were analyzed without the system suitability being verified at the actual condition of use. The analysis sequence included test sample from batch HE00004 and HE00005 of SDD product manufactured at your Cork site. The batch HE00004 and batch HE00005 were manufactured as part of the demonstration on SDD product reprocessing.

Material

OBSERVATION 5:

Your firm's product labeling practice is deficient that had resulted in incorrect retest date shown on the internal product drum labels. Specifically,

During warehouse walkthrough inspection on 16May2016, 15 drums of SDD product batch HE00004 were observed to have drum labels showing retest date of 01May2016. Upon verifying the SAP record, it was found that the actual retest date of this product batch was 19Apr2016. Therefore the retest date for the same product lot was different between the product labels on the drums and the SAP record.

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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 judgement, 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 insanitary 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."