Health Care Inspectorate - Pharmaceutical Affairs and Medical Technology

Report No: ***NL/H 15/1004683***

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer [1]

Part 1

Issued following an inspection in accordance with :
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of Netherlands confirms the following:
The manufacturer: ***INTEGRA LIFE SCIENCES CORP***
Site address: ***105 MORGAN LANE, PLAINSBORO, 08356, United States***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-04-16*** , it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC

[1] *The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.*

Part 2

Human Medicinal Products

1 NON-COMPLIANT MANUFACTURING OPERATIONS	
Include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.4 Impregnated matrices
1.5	**Packaging**
	1.5.1 Primary Packing 1.5.1.4 Impregnated matrices
1.6	**Quality control testing**
	1.6.2 Microbiological: non-sterility *1.6.3 Chemical/Physical*

Part 3

1. Nature of non-compliance:
1. Contamination of Absorbable Collagen Sponges with particulate matter is not under control. ACS sheets are exposed to an ISO Class 7 environment without protection by Grade A air. This is relevant during the loading and unloading of the cross-linking chamber, the cutting of the sponges, the visual inspections and the (re)packaging stage. Embedded particles do occur but are not always removed during visual inspection if seen. During visual inspection tweezers are used constantly to remove visible contaminants from the surface of sponges. This is regarded by the company as a part of routine production. A comprehensive analysis of the root cause of contamination is not conducted. Packaging material seems to be a source of foreign matter, but other than vacuuming trays before packaging (which proved to be insufficient) no preventive measures have been taken. Static charges contribute to the problem of particulate matter contamination, as was seen by a hair that was stuck on the outside of a container used to store sponges for a long time. The design and functioning of the sponge cutting table as a source of particulate contaminants has not been considered. 2. The quality system is not aiming for continuous improvement; manufacturing processes are not designed in a way that product quality is achieved consistently: extensive corrective inspections are performed, repackaging of a significant number of units is routinely necessary due to quality defects, and rejection of significant parts of the batches is accepted as normal. An investigation initiated to improve the process is defective: contaminants removed during the visual inspection of unpackaged sponges are left out of the investigation, which is limited anyway to 2 batches only without proper justification.

Action taken/proposed by the NCA

Prohibition of supply
Applies to batches of InductOs released after 16 April 2015

Additional comments
Integra LifeSciences is the manufacturer of Absorbable Collagen Sponge that forms an integral part of InductOs, EU/1/02/226/001, kit for implant. This kit consist of the active substance dibotermin alfa as a sterile powder, a solvent and the ACS matrix. Prior to implantation the active substance will be dissolved and dispensed onto the matrix. Inspection history: GMP Inspection January 2014 by NL and SP under INS/GMP/2013/036 TruScient, kit for implant (for use in dogs) and INS/GMP/2013/037 InductOs, kit for implant (for use in humans). Result GMP non-compliant. Main concerns were particulate contamination and sterility assurance. A Corrective Action Plan was received April 2014, which was rejected by inspectors. A new plan was received May 2014. This was accepted and a restricted GMP certificate was issued valid until January 2015. Re-inspection was done by the same inspectors from NL and SP in April 2015 under INS/GMP/2014/078 InductOs, kit for implant (TruScient was cancelled). Result again GMP non-compliant. The main concern was still particulate contamination. Corrective Action Plan received June 2015 which was rejected by inspectors. This rejection is based upon lack of clarity on the nature and extent of particulate contaminants. Metal fragments, salt residues, hairs and PVC fibers are identified, but for none of these the most likely source has been established. No new GMP certificate was issued. Status of product: Absorbable Collagen Sponge is part of a kit which contains dibotermin alfa as the active substance. The sponge on it's own is marketed in CY, FR, D, GR, IT, PL, SP under the brand name Helitene as a hemostatic medical device for external use under a CE mark issued by notified body BSI. In the USA the combination of dibotermin alfa and ACS is regulated as a medical device. MAH of InductOs is Medtronic BioPharma B.V. in Heerlen, The Netherlands. The company is represented by Granzer Regulatory Consulting & Services in München, Germany.

2015-07-23

Name and signature of the authorised person of the Competent Authority of Netherlands

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