French National Agency for Medicines and Health Products Safety

Report No: ***15MPP060HFR01NCS***

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 France confirms the following:
The manufacturer: ***CARGILL FRANCE***
Site address: ***ZI Menez Bras, LANNILIS, 29870, France***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-07-24*** , it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles of GMP for active substances referred to in Article 47 of Directive 2001/83/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

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) 1.2.1.17 Other: active substance(en)

Manufacture of active substance. Names of substances subject to non-compliant :
ALGINIC ACID(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : ALGINIC ACID	
3.2	**Extraction of Active Substance from Natural Sources**
	3.2.1 Extraction of substance from plant source 3.2.6 Purification of extracted substance Plant
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Milling, Sieving 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

Part 3

1. Nature of non-compliance:

Overall, 14 observations were made, including 1 critical deficiency and 4 major deficiencies: [Critical] The management of semi-finished batches and of the mixing operations was deficient and conformity of the final batches to specifications, notably Ph.Eur. specifications, could not be guaranteed. [Major 1] The site had been manufacturing an active substance without ANSM authorisation. [Major 2] The change control related to the suppression of one filtration step in the active substance manufacturing process was deficient. [Major 3] The manufacturing of the active substance had not been made using master production instructions and no batch production records had been established. [Major 4] No review of batch production records of critical process steps had been done before release of the active substance for distribution. 7 observations are related to lack of traceability, risks of contamination induced by the absence of cleanliness in the production environment, very bad condition of the production equipment and insufficient equipment cleaning procedures. The inspection's observations also apply to the manufacture of pharmaceutical excipients and starting materials that are intended to be used as ingredients in cosmetics and medical devices, which are manufactured under the same conditions as the active substance.

Action taken/proposed by the NCA

Recall of batches already released
See additional comments section. It has to be noted that ANSM did not issue a recall for all health products. The decision of sanitary police expects that the concerned marketing holders must perform a QRM regarding the quality

and safety of their products to support the absence of recall of batches already released on the market and/or the distribution of these products. >>> In the case of medicines, the QRM report has to be addressed to the NCAs where the products are marketed. <<< Cargill France at the Lannilis site had manufactured only one active substance, i.e. alginic acid. This substance had been used by Pierre Fabre Medicament/ PFM (Gien, France) for the manufacture of Topaal : - Topaal oral suspension PFM already stopped the commercialisation of this medicine on 5 January 2015 (an internal company decision) Based on the fact that the active substance had not been manufactured in an authorised site, that this site was not GMP Part II compliant, and that the specification of the finished product was not compliant to Ph.Eur., PFM, in agreement with ANSM, has decided to recall the remaining batches on the market. - Topaal tablets PFM already stopped the commercialisation of this medicine on 27 August 2015 (internal company decision). Based on the fact that the active substance was not manufactured in an authorised site and that this site was not GMP Part II compliant, PFM, in agreemnent with ANSM, has decided to recall the remaining batches on the market. - The two recalls were effective on 5 october 2015 (A rapid alert class II has been sent to the concerned NCA).

Prohibition of supply
See additional comments section.

Additional comments
A sanitary police decision was issued by ANSM on 25 September 2015 to suspend the manufacturing, packaging, licensing, distribution, exportation, and the use of the starting materials (notably alginic acid and alginates) manufactured by Cargill France at the Lannilis site that are intended to be used as ingredients in medicines, cosmetics and medical devices. The decision has been published on the ANSM website on 29 September 2015 and is valid for not more than one year, according to the French regulation. (http://ansm.sante.fr/Decisions/Injonctions-decisions-de-police-sanitaire-interdictions-de-publicite-Decisions-de-police-sanitaire). As part of the contradictory procedure, the sanitary police decision has already been communicated to the identified Cargill's customers (Lannilis site) in the field of medicines, cosmetics and medical devices which contain ingredients manufactured by this site (in France and outside France).

2015-10-30

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

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