National Agency For The Safety Of Medicine And Health Products

Report No: ***22MPP077NCR***

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. 94(2) of Regulation (EU) 2019/6 as amended
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of France confirms the following:
The manufacturer: ***Givaudan-Lavirotte***
Site address: ***56 Rue Paul Cazeneuve, Lyon, 69008, France***
OMS Organisation Id. / OMS Location Id.: ***ORG-100019365*** / ***LOC-100028130***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2022-10-21***, 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 (EU) 2017/1572 and Commission Delegated Regulation (EU) 2017/1569 and Article 47 of Directive 2001/83/EC
- The principles and guidelines of Good Manufacturing Practice laid down in Directive 91/412/EC Article 93(2) of Regulation (EU) 2019/6
- 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;	
1.4	**Other products or manufacturing activity**
	1.4.1 Manufacture of 1.4.1.3 Other: Active substances(en)

Manufacture of active substance. Names of substances subject to non-compliant:

MAGNESIUM GLUCOHEPTONATE(en)
GLYCEROPHOSPHORIC ACID 50%(en)
MAGNESIUM GLUCONATE(en)
MAGNESIUM GLYCEROPHOSPHATE 50%(en)
SODIUM GLYCEROPHOSPHATE 50%(en)
SODIUM GLYCEROPHOSPHATE 65%(en)
CALCIUM GLYCEROPHOSPHATE 50%(en)
POTASSIUM GLYCEROPHOSPHATE 50%(en)
POTASSIUM GLYCEROPHOSPHATE 75%(en)
ZINC GLUCOHEPTONATE(en)
BENZYL NICOTINATE(en)
CALCIUM GLUCOHEPTONATE(en)
CALCIUM LACTATE GLUCONATE(en)
CALCIUM GLYCEROPHOSPHATE(en)
COPPER GLUCONATE(en)
ETHYL NICOTINATE(en)
IRON GLUCOHEPTONATE(en)
FERROUS GLUCONATE(en)
MANGANESE GLUCONATE(en)
CALCIUM GLUCONOGLUCOHEPTONATE(en)
HEXYL NICOTINATE(en)
LITHIUM GLUCONATE(en)
MAGNESIUM GLYCEROPHOSPHATE(en)
METHYL NICOTINATE(en)
NICOTINAMIDE(en)
UNDECYLENIC ACID(en)
ZINC GLUCONATE(en)
ZINC UNDECYLENATE(en)

Clarifying remarks (for public users)

Calcium glucoheptonate : not intended for use in injectable forms / Iron glucoheptonate : not intended for use in injectable forms / Magnesium glucoheptonate : not intended for use in injectable forms / Zinc glucoheptonate : not intended for use in injectable forms / Calcium gluconoglucoheptonate : not intended for use in injectable forms / Zinc gluconate : not intended for use in injectable forms / Magnesium gluconate : not intended for use in injectable forms / Ferrous gluconate : not intended for use in injectable forms / Copper gluconate : not intended for use in injectable forms / Manganese gluconate : not intended for use in injectable forms

Part 3

1.Nature of non-compliance:

During this inspection, 15 deficiencies were observed, out of which 10 were classified as major // E1[Major] : failures related to deviation management // E2[Major] : insufficient documentation of the quality risk related to the temporary cessation of the company's activities between April 10th, 2022 and July 29th, 2022 // E3[Major] : insufficient quantity of staff, particularly concerning Quality Assurance and Qualification-Validation activities // E4[Major] & E5[Major] : major defects in the design and maintenance of all the facilities inspected // E7[Major] : multiple and repeated failures in the cleaning of equipment used for the manufacture of starting materials for pharmaceutical use, concerning all inspected workshops // E8[Major] : failures concerning traceability of the operations performed on equipment // E9[Major] : multiple and repeated deficiencies in the upkeep and maintenance of equipment used for the manufacture of starting materials for pharmaceutical use // E12[Major] : repeated weaknesses in the correction of anomalies related to equipment qualifications // E15[Major] : shortcomings in the management of cross-contamination risks, highlighted by deficiencies in the verification of the effectiveness of the cleaning methods applied in the multi-product workshops

Action taken/proposed by the NCA

Prohibition of supply
After issuance of the non-compliance report and as long as it remains active, the site should not be authorized to distribute starting materials for pharmaceutical use

Suspension or voiding of CEP (action to be taken by EDQM)
EDQM to consider the suspension of several CEPs : CEP 2016-127 (Calcium glucoheptonate) // CEP 1996-106 (Calcium glycerophosphate) // CEP 1999-164 (Ferrous gluconate hydrate) // CEP 2012-221 (Zinc gluconate)

Additional comments
The validity date of the last GMP certificates (21MPP011HVFR01 and 21MPP011VFR01) and GDP certificate 21MPP011D01 is February 28th, 2023 // No recall of products should be considered. // Where such a MA exists, the addition of an alternative supplier to the MA should be considered using quality risk management (QRM) principles // A sanitary police decision was issued by ANSM on July 3rd, 2023 to suspend manufacturing, importation and distribution activities, including those for export, concerning active substances and manufacturing, packaging, marketing, distribution and exportation activities concerning excipients manufactured by the company GIVAUDAN-LAVIROTTE on the site of Lyon (France), and intended for use in the composition of medicinal products. The decision has been published on the ANSM website on July 10th, 2023. As part of the contradictory procedure, the sanitary police decision has already been communicated to the identified Givaudan-Lavirotte customers in the field of human medicines which contains ingredients manufactured by this site (in France and outside France)

2023-07-11

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

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Confidential
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