Italian Medicines Agency

Report No: ***IT/NCR/API/1/2018***

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 Italy confirms the following:
The manufacturer: ***LAMPUGNANI FARMACEUTICI SPA***
Site address: ***Via Gramsci, 4, via Ticino, NERVIANO, 20014, Italy***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2018-05-24*** , 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;	
1.4	**Other products or manufacturing activity**
	1.4.3 Other: manufacture of active substances(en)

Manufacture of active substance. Names of substances subject to non-compliant :
DEFEROXAMINA MESILATO STERILE(it) / DEFEROXAMINE MESILATE STERILE(en)
ERITROMICINA GLUCOEPTONATO STERILE(it) / ERYTHROMYCIN GLUCEPTATE STERILE(en)
FRAMICETINA SOLFATO STERILE(it) / FRAMYCETIN SULFATE STERILE(en)
IDROCORTISONE SODIO FOSFATO STERILE(it) / HYDROCORTISONE SODIUM PHOSPHATE STERILE(en)
IDROCORTISONE SODIO SUCCINATO STERILE(it) / HYDROCORTISONE SODIUM SUCCINATE STERILE(en)
KANAMICINA SOLFATO ACIDO STERILE(it) / KANAMYCIN ACID SULFATE STERILE(en)
STREPTOMICINA SOLFATO STERILE(it) / STREPTOMYCIN SULFATE STERILE(en)
TEICOPLANINA STERILE(it) / TEICOPLANIN STERILE(en)
TIOPENTALE SODICO E SODIO CARBONATO STERILE(it) / THIOPENTAL SODIUM AND SODIUM CARBONATE STERILE(en)
VANCOMICINA CLORIDRATO STERILE(it) / VANCOMYCIN HYDROCHLORIDE STERILE(en)
DIIDROSTREPTOMICINA SOLFATO STERILE(it) / DIHYDROSTREPTOMYCIN SULFATE STERILE(en)
ERITROMICINA LATTOBIONATO STERILE(it) / ERYTHROMYCIN LACTOBIONATE STERILE(en)
FRUTTOSIO 1.6 DIFOSFATO SALE SODICO STERILE(it) / FRUCTOSE 1,6-BISPHOSPHATE SODIUM SALT STERILE(en)
GLUTATIONE SODICO STERILE(it) / GLUTATHIONE SODIUM STERILE(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : DEFEROXAMINE MESILATE STERILE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.4 Other : Dissolution
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : ERYTHROMYCIN GLUCEPTATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : salt formation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : FRAMYCETIN SULFATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.4 Other : Dissolution
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : HYDROCORTISONE SODIUM PHOSPHATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**

	3.1.4 Other : Ultrafiltration *Special Requirements:* 7. Other : hormones or substances with hormaonal activity
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : HYDROCORTISONE SODIUM SUCCINATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : salt formation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : KANAMYCIN ACID SULFATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.4 Other : Dissolution
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared

3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : STREPTOMYCIN SULFATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.4 Other : Dissolution
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : TEICOPLANIN STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.4 Other : Dissolution
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : THIOPENTAL SODIUM AND SODIUM CARBONATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : salt formation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : VANCOMYCIN HYDROCHLORIDE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : salt formation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : DIHYDROSTREPTOMYCIN SULFATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**

	3.1.4 Other : Dissolution
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : ERYTHROMYCIN LACTOBIONATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : salt formation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : FRUCTOSE 1,6-BISPHOSPHATE SODIUM SALT STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : salt formation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Active Substance : GLUTATHIONE SODIUM STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : salt formation 3.1.4 Other : Dissolution
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : lyophilisation, 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)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Part 3

1. Nature of non-compliance:

Major deficiencies were found in the following areas: Premises/equipment (9): Deficiencies found in monitoring the controlled contamination areas and Deficiencies found in the status of Premises/Equipment and personnel/material flows. Production (1): Deficiencies were observed during the aseptic manufacturing operations in the production areas. Microbiological quality control testing (2) Personnel (1) Deviation management (1) These major deficiencies are mainly referring to the aseptic production and quality control which constitutes a critical risk for public health due to the lack of sterility assurance of the drug substances.

Action taken/proposed by the NCA

Recall of batches already released

If there are alternative suppliers and there is no risk of shortage, recall of medicinal products manufactured using APIs aseptically lyophilised by Lampugnani should be evaluated by involved NCAs' following assessment conducted in conjunction with MAHs.

Prohibition of supply

Prohibition of supply of APIs aseptically lyophilized by Lampugnani is recommended. Lack of alternative suppliers

and risk of shortage should be assessed case by case.

Suspension or voiding of CEP (action to be taken by EDQM)
Since Lampugnani Farmaceutici is a contract manufacturer carrying out the lyophilisation in aseptic conditions of APIs manufactured by other Companies, information about the CEP are not currently available.

Others
The Company holds authorization for manufacturing sterile APIs and registration for non sterile APIs. The Company holds also a MIA for finished dosage operations (storage, quality control testing: chemical/physical and microbiological testing, excluding sterility testing). Proposed actions: 1. Authorization for production of sterile APIs to be suspended 2. Registration for production of non-sterile APIs to be maintained as the Statement of non-compliance does not impact the non-sterile APIs manufactured at the site. 3. MIA for finished dosage forms (storage, quality control testing: chemical/physical and microbiological testing - sterility testing excluded) to be maintained as the GMP-non compliance statement does not have an impact on non-sterile products GMP certificate related to APIs for human use will be updated removing all sterile APIs. No impact on the GMP certificate related to finished dosage forms and non sterile APIs. This Contract manufacturer for aseptic lyophilisation should not be approved in any new/ongoing applications until appropriate corrective actions will be implemented and GMP compliance will be resumed. The CAPA plan provided by the Company was evaluated by AIFA; all the responses were considered acceptable; however, due to the seriousness of the deficiencies, AIFA is planning a follow-up inspection in a short timeframe, for an on-site evaluation of the implementation and suitability of the CAPA and, in case of positive outcome, the withdrawal of the statement of GMP non compliance with re-issuance of the GMP certificate covering also the sterile APIs; currently, AIFA is going to issue the GMP certificate only for Drug products (for storage and quality control testing, excluding sterility testing) and non sterile APIs.

Additional comments
The Statement of non-compliance also impacts on the active substances for veterinary use: DIHYDROSTREPTOMYCIN SULFATE STERILE and FRAMYCETIN SULFATE STERILE.

2018-07-17

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

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