Italian Medicines Agency

Report No: ***IT/NCR/API/1/2019***

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: ***FARMABIOS S.P.A.***
Site address: ***Via Pavia, 1, GROPELLO CAIROLI, 27027, Italy***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2019-09-20*** , 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 :

BECLOMETASONE DIPROPIONATE STERILE(en)
BUDESONIDE STERILE(en)
HYDROCORTISONE ACETATE STERILE(en)
LOTEPREDNOL ETABONATE STERILE(en)
METHYLPREDNISOLONE ACETATE STERILE(en)
PREDNISOLONE ACETATE STERILE(en)
TRIAMCINOLONE ACETONIDE STERILE(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance : BECLOMETASONE DIPROPIONATE STERILE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture of active substance intermediates *Special Requirements:* 7. Other : Hormones or substances with hormonal activity 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, micronisation 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

Active Substance : BUDESONIDE STERILE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture of active substance intermediates

	Special Requirements: 7. Other : Hormones or substances with hormonal activity 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, micronisation 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

Active Substance : HYDROCORTISONE ACETATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates *Special Requirements:* 7. Other : Hormones or substances with hormonal activity 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, micronisation 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

Active Substance : LOTEPREDNOL ETABONATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates

	Special Requirements: 7. Other : Hormones or substances with hormonal activity 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, micronisation 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

Active Substance : METHYLPREDNISOLONE ACETATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2 Manufacture of crude active substance *Special Requirements:* 7. Other : hormones or substances with hormonal activity 3.1.3 Salt formation / Purification steps : crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, micronisation 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 3.6.4 Biological Testing

Active Substance : PREDNISOLONE ACETATE STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates

	Special Requirements: 7. Other : Hormones or substances with hormonal activity 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, micronisation 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
Active Substance : TRIAMCINOLONE ACETONIDE STERILE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates *Special Requirements:* 7. Other : Hormones or substances with hormonal activity 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, micronisation 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 3.6.2 Microbiological testing excluding sterility testing 3.6.4 Biological Testing

1. Nature of non-compliance:
30 deficiencies were found, 10 classified as “Major” in the following areas: - Premises/equipment (4) - Production (2) - Quality control (3) - Personnel (1) Six out of ten 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 API manufacturing suppliers and there is no risk of shortage, recall of medicinal product manufactured using APIs aseptically manufactured by Farmabios should be evaluated by involved NCAs following assessment conducted in conjunction with the concerned MAHs. **Prohibition of supply** Prohibition to use APIs aseptically manufactured by Farmabios is recommended. Lack of alternative service providers and risk of shortage should be assessed case by case. **Suspension or voiding of CEP (action to be taken by EDQM)** Suspension of CEP (RO-CEP2017-286-Rev 00). for the active substance Prednisolone acetate micronised sterile should be considered **Others** The Company holds authorization for manufacturing sterile APIs and registration for non sterile APIs. Proposed actions: 1. Authorisation for production of aseptically manufactured sterile APIs to be suspended. Authorisation for APIs sterilized by gamma irradiation to be maintained as the statement of non compliance does not impact the gamma irradiation that is performed by a contract manufacturer. 2. Registration for production of non-sterile APIs to be maintained as the statement of non compliance does not impact the not sterile APIs manufactured at the site. The GMP certificate for non sterile APIs and for sterile APIs sterilized by gamma irradiation will be issued after favourable conclusion of the CAPA evaluation.
Additional comments BECLOMETASONE DIPROPIONATE STERILE is sterilized by filtration under aseptic condition or alternatively by gamma irradiation. Other sterile APIs manufactured with final sterilization by gamma irradiation is MEDROXYPROGESTERONE ACETATE STERILE. The statement of non-compliance also impact on the active substances of veterinary use: PREDNISOLONE ACETATE STERILE and PREDNISOLONE STERILE

2019-11-22

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

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