Agency for Medicinal Products and Medical Devices of Croatia

Report No: ***UP/I-530-10/19-03/31; 381-10-05/243-19-03***

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 Croatia confirms the following:
The manufacturer: ***NCPC HEBEI HUAMIN PHARMACEUTICAL CO., LTD.***
Site address: ***No. 98 Hainan Road, Economic and Technological Development Zone, Shijiazhuang, Hebei Province, 052 165, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2019-09-06*** , 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 :
CEFOTAXIME SODIUM STERILE(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance : CEFOTAXIME SODIUM STERILE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallisation, filtration-washing-drying
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared *Special Requirements:* 1. B-lactam antibiotics
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : grinding, sieving, homogenisation 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 3.6.3 Microbiological testing including sterility testing

Any restrictions related to the scope of this statement :

Building	Room	Line/equipment	QC testing	Products
Workshop No. 103		***Line C***		

Clarifying remarks (for public users)

This inspection was performed jointly with EDQM in connection with CEP 2014-197/Cefotaxime sodium, sterile

Part 3

1. Nature of non-compliance:

This inspection was carried out in the framework of the EDQM inspection programme on 2 – 6 September 2019. Scope of the inspection was Cefotaxime sodium, sterile (CEP 2014-197). The inspection revealed 31 deficiencies in total. Out of 31 deficiencies, two were classified as critical deficiencies and five as major deficiencies. One other deficiency was considered as non-conformity to the CEP dossier 2014-197/Cefotaxime sodium, sterile. The critical deficiencies were related to aseptic manufacturing operations (Workshop No. 103, Line C): microbiological environmental monitoring and preparation, sterilisation and usage of sterile disinfectants in the aseptic manufacturing facilities. The major deficiencies were found in the areas of: quality assurance (implementation of CAPA after the last EDQM inspection); control of documentation; preparation and handling of sterile primary packaging material; electronic records and signature; manufacturing areas and equipment.

Action taken/proposed by the NCA

Requested Variation of the marketing authorisation(s)
This manufacturer should not be authorised in any new/ongoing marketing authorization or variation applications for the sterile active pharmaceutical ingredients under the non-compliance statement. The submission of a variation application for introducing alternative manufacturers of the active ingredients is recommended.

Recall of batches already released
A recall of medicinal products should be evaluated by involved NCAs' following the assessment with marketing authorisation holders.

Prohibition of supply
Prohibition of supply of Cefotaxime sodium sterile, Cefuroxime sodium sterile and Ceftriaxone sodium sterile is recommended, unless there are no alternative suppliers and there is a risk of shortage.

Suspension or voiding of CEP (action to be taken by EDQM)
Suspension of CEPs: CEP 2014-197/Cefotaxime sodium, sterile; CEP 2014-021/Cefuroxime sodium, sterile

Others
The same regulatory actions are proposed for Cefotaxime sodium sterile, Cefuroxime sodium sterile and Ceftriaxone sodium sterile, as all three APIs are manufactured at the same workshop and production line (Workshop No. 103, Line C).

2019-11-07

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

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Ms. Ljubica Hodak Buric
Agency for Medicinal Products and Medical Devices of Croatia
Tel: ***+385 1 4884143***
Fax: ***+385 1 4884110***