Italian Medicines Agency

Report No: ***IT/NCR/API/3/2014***

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: ***Fujian South Pharmaceutical***
Site address: ***No. 98 Dongxin Road. Xuefeng Town. Mingxi, Fujian, 365200, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2014-09-06*** , 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**
	1.4.1 Manufacture of 1.4.1.4 Other: Active Substances(en)

Manufacture of active substance. Names of substances subject to non-compliant :
DOCETAXEL ANIDRO(it) / DOCETAXEL ANHYDROUS(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES Active Substance : DOCETAXEL ANHYDROUS	
3.2	**Extraction of Active Substance from Natural Sources**
	3.2.5 Modification of extracted substance Plant 3.2.6 Purification of extracted substance Plant
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, milling 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

Part 3

1. Nature of non-compliance:

In total 27 deficiencies were found by the inspection team, whose opinion is that two of them constitute a risk to the patient and were hence categorised as critical and related to the Quality Control System and to the implementation of sound computerised systems, including data integrity issues. Furthermore three major deficiencies were observed in the field of building and facilities, documentation and laboratory controls. Here below a brief summary of the Critical and Major deviations: [Critical] The inspection team tried to verify some regulatory information requested during the assessment of the dossier and reached the conclusion that fundamental GMP and regulatory requirements such as loss of data integrity, combined with insufficient management of data, change control system, supplier qualification, laboratory controls as well as the accuracy of data submitted, were not adequately implemented/considered because of a weakness of the QA system and regulatory affairs department; [Critical] Severe GMP violations related to the implementation of sound computerised systems in the quality control facilities were committed, that could lead/could have led to the falsification of data. It was impossible to verify that the decision to approve raw material and final API was based on valid and accurate data; [Major] In workshop B-03 the room used to perform the first purification of Docetaxel anhydrous by liquid chromatography was found not suitable for its intended use, as there was a potential risk of contamination; [Major] The issuance of quality related documentation was found inadequately controlled/secured by QA; [Major] The Company's manufacturing process C for Docetaxel anhydrous requires the blending of individual batches. The insufficient equipment capacity requires the material previously obtained to be split into two single batches. The manufacturing operations to be conducted in the final purification step are four crystallisations followed by drying. No testing of the individual batches was required prior to the blending operation. This approach could lead to masking of Out-of-Specification results in the individual batches. The remaining 22 deficiencies identified some additional issues in the field of Quality Management, Buildings and Facilities, Process Equipment, Documentation and Records, Laboratory Controls, Validation, Rejection and Re-use of Materials.

Action taken/proposed by the NCA

Prohibition of supply

Due to the nature of non-compliances, prohibition of supply is recommended.

Suspension or voiding of CEP (action to be taken by EDQM)

The EDQM Ad Hoc Committee decided to suspend the certificate of suitability CEP 2011-320 (Docetaxel anhydrous).

Additional comments

This inspection was performed in the framework of the EDQM inspection programme (EDQM inspection procedure number: INSP 2014-001 P01). According to the information gathered during the inspection, so far only samples have been supplied to EU/US customers; the main market for the Company's products is China. No information was obtained as to whether contract manufacture for MAA in EU was concerned.

2014-10-29

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

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