Italian Medicines Agency

Report No: ***IT/NCR/API/3/2015***

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: ***WUXI JIDA PHARMACEUTICAL CO., LTD***
Site address: ***No. 2, Qiancun Road, Cheng Chang Industry Park Huangtu Town, Jiangsu Province, Jiangsu City, 214445, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-06-11*** , 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 :
STERILE GLUTATHIONE SODIUM LYOPHILISED(en)

Part 3

1. Nature of non-compliance:

The inspection was performed by GMP inspectors in relation to the manufacture of sterile glutathione sodium lyophilised object of a variation. The inspection was focused on site 1 and production workshop number 3. During the inspection 28 deficiencies were found, 15 of which were rated as major deficiencies. Major Deficiencies: In many production steps deviations were found regarding the sterility assurance and a risk of contamination of the product: a) Sampling room (deviations 14-15-16): the changing room was not designed in a suitable way to minimize the risk of contamination; the differential pressure between the areas maintained at different cleanliness grade was not monitored; the garments procedure was not in accordance to the principle of classified areas; b) Production areas (deviations 19-20-21-24): the pressure differential between adjacent areas at different cleanliness grade was not in compliance with the guidance value of the European good manufacturing practices; the maintenance and cleaning conditions of some production rooms were poor and not adequately handled; the particle counters in B class grade (i.e. freeze-dryers and capping room) were unsuitable located for the intended use; the API transfer from the mixer to aluminum tin did not exclude a risk of API contamination. c) Validation (deviation 7 from letter a to j): the validation approach for different activities was not correctly performed according to the GMP requirements and validation reports were not detailed (warehouse temperature mapping; holding time for sterilization of tools; stay-time in UV-pass box; maximum number of filters sterlisation (20) validation for the moist heat sterilizer used for the rubber stopper sterilization; validation for the dry heat steriliser used for the aluminium tin sterilisation; validation for LAF in weighing room; validation for the HVAC of the sampling room; validation for front-freezing room classification; validation report for the process simulation namely maximum filling time of loading the bulk product in freeze-dryers and maximum time of transferring API from mixer to aluminum tins and capping. d) Packaging and labeling (deviations 5-10-11-13): the management for the container closure system for sterile glutathione sodium freeze-dried was found lacking in some tests to guarantee the sterility assurance of the product; a “wrong“ and not-updated label was used as a standard to verify the shipping labels of API; in the API warehouse, the aluminum tins of sterile API were not sealed; the aluminum caps were not identified with a batch number loosing traceability. e) Laboratory testing (deviation 28): some deviations were found for the IR instrument, in particular the IR software had not a controlled access via ID and password and it was not forbidden to copy and rename a file. f) Personnel behavior (deviations 2-7i(ii)-18-19): during the inspection, the inspectors’ team received inconsistent and conflicting answers on the same topic from both personnel and management; sometimes the answers seemed to be modified according to the inspectors’ requests. The documentation was showed in an ambiguous way as the examples: some layouts were replaced; some documentation was unrelated to the topic. Finally management did not comply with the clothing procedure during the inspection tour.

Action taken/proposed by the NCA

Recall of batches already released
Each involved NCA should evaluate, following assessment conducted in conjunction with MAHs, if a recall of medicinal product is needed. Evaluation should take into account if there are alternative suppliers and potential risk of shortage. Given the nature of non-compliances, assessment should include a complete retest of all imported batches of

active substance.

Prohibition of supply
Due to the nature of non compliance, prohibition of supply is racommended.

Others
This supplier should not be approved in any new / ongoing applications. Each involved NCA should evaluate if the supplier should be removed from existing MAs.

2015-07-28

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

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