Italian Medicines Agency

Report No: ***IT/NCR/API/2/2018***

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: ***ZHEJIANG HUAHAI PHARMACEUTICAL CO. LTD***
Site address: ***Chuannan Duqiao, Linhai, Zhejiang, 317016, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2018-09-13*** , 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 :
VALSARTAN(en) / VALSARTAN(fr) / ВАЛСАРТАН(bg) / WALSARTAN(pl) / VALSARTANUM(cs)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : VALSARTAN	
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
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : physical processing steps performed 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

Part 3

1. Nature of non-compliance:
The joint EMA/EDQM inspection was initiated as “for-cause” inspection in the context of the NDMA/NDEA Valsartan contamination issue. Nine “Major” and eight “Other” deviations were identified. The Major deficiencies were found in the following areas: 1. The investigations conducted in the context of the NDMA/NDEA contamination of Valsartan showed significant flaws; 2. The company’s risk assessment performed in the context of the development/implementation of the optimised Valsartan process, conducted in July/August 2018, was not satisfactory; moreover, the company did not identify the need to develop a control strategy to reduce the new risks introduced with the optimised process; 3. Several gaps were identified in the context of the development of the Valsartan process as revised in 2011/2012. N.B.: the changes introduced with this modified process led to the formation of the NDMA impurity; 4. Observations related to the handling of the complaints, with specific focus on the NDMA contamination issue; 5. Management of out-of-specification results; 6. Recall management: no recall was formally initiated to manage the actions related to the contaminated Valsartan batches; 7. Reprocessing/blending operations including traceability of reprocessed/blended material ; 8. Data integrity issues in relation to GC-FID analysis; 9. Inadequate investigation of unknown peaks detected in GC-MS analysis of batches of Valsartan manufactured with the new process as optimized in July/August 2018.

Action taken/proposed by the NCA

Requested Variation of the marketing authorisation(s)
Actions on Marketing Authorisations should be assessed by the respective licensing authority covering MAs which include Valsartan and Valsartan intermediates manufactured by the inspected firm

Recall of batches already released
Recalls of products containing Valsartan API manufactured by the company have already been conducted in EU

Prohibition of supply
The company has already been prohibited to supply Valsartan to the EU market

Suspension or voiding of CEP (action to be taken by EDQM)
CEP 2010-072 for Valsartan was already suspended. It is recommended to consider actions related to other Valsartan CEPs in which the inspected company is mentioned as intermediate manufacturer

Others
It is recommended to prohibit also supply of Valsartan intermediates to the EU market

Additional comments
The for-cause inspection focused on Valsartan, therefore the non-compliance statement is restricted to this API.

2018-09-28

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

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