Spanish Agency of Medicines and Medical Devices

Report No: ***INS/GMP/2018/111; INS/GMP/2018/112; INS/GMP/2019/063 and INS/GMP/2019/064.***

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
Art. 80(7) of Directive 2001/82/EC as amended

The competent authority of Spain confirms the following:
The manufacturer: ***ZHEJIANG HISUN PHARMACEUTICAL, Co., Ltd. (EAST FACTORY CAMPUS)***
Site address: ***1 HAIZHENG ROAD, JIAOJIANG DISTRICT, TAIZHOU, CN-318000, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2019-03-26*** , 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 and Article 51 of Directive 2001/82/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)

4. Non-Compliant Other Activities - Active Substances :

The non-compliance statement applies to the following active pharmaceutical ingredients (API) which are manufactured in the building E08 (docetaxel trihydrate, bortezomib and fludarabine phosphate). Manufacturing of any cytotoxic/hazardous products, and not limited to the cytotoxic/hazardous products manufactured in the building mentioned above or in any new building, should be carried out only after a follow-up inspection has been conducted.

Part 3

1. Nature of non-compliance:

Overall 25 deficiencies were identified during the inspection, 2 critical and 5 major. The critical deficiencies detected were motivated by a deficient handling of non-cytotoxic, cytotoxic, hazardous and highly potent substances in multi-product facilities (i.e. mainly in buildings Y36, Y37, Y38, Y39 at Yantou Campus and E08 at East Factory Campus, but also other buildings could pose some risks, such as Y20, Y33, Y35, Y50 at Yantou Campus). Risk of cross contamination in these facilities had not been properly identified and mitigated. The major deficiencies observed were identified in the cleaning validation, purified water monitoring, intermediate hold-time validation, recovering solvent process.

Action taken/proposed by the NCA

Requested Variation of the marketing authorisation(s)

1.This manufacturer should not be authorised in any new/ongoing marketing authorization or variation applications for the active pharmaceutical ingredients under the non-compliance statement. 2. The submission of a variation application for introducing alternative manufacturers of the active ingredients is recommended.

Recall of batches already released

Since the activity at the site for EU market was already suspended as a consequence of the 2016 non-compliance statements, and only critical active pharmaceutical ingredients have been manufactured and imported to EU, no recall of the active ingredients manufactured in the site is presently recommended. However, in case out of specification results (OOS) are obtained as a result of testing recommended as interim measure B, these results should be communicated by MAH to NCA. The decision to be made by NCA, following an assessment between the NCA and MAH, whether to recall a batch of a particular product or not should be based on a risk assessment and on the criticality of the product. Evaluation should take into account if there are alternative suppliers and potential risk of shortage. The Compilation of Community Procedures on Inspections and Exchange of Information (CoCP) (i.e. non-compliance, recall) should be followed.

Prohibition of supply

Prohibition of supply of the API listed above is recommended, unless there are not alternative suppliers and there is a risk of shortage.

Others

Due to the number and severity of the findings detected, the following additional measures are recommended: A. Statements of Non-compliance with GMP should be issued for the active ingredients listed above and manufactured in

buildings Y20, Y33, Y35, Y36, Y37, Y38, Y39, Y50 at Yantou Campus and E08 at East Factory Campus. Manufacturing of any cytotoxic/hazardous products, and not limited to the cytotoxic/hazardous products manufactured in the building mentioned above or in any new building, should be carried out only after a follow-up inspection has been conducted. B.To oblige medicinal product manufacturers located both in EU and third countries to perform full analytical testing of every batch of active substances manufactured at Hisun and listed above, including impurities, residual solvents and microbial burden. Member States should collect and monitor the information gathered as a result of the enhanced analytical testing. This measure is not applicable for batches that are currently on the market.

Additional comments

Marketing autohorisation holders are requested to contact the relevant National Competent Authority to verify wheter the API listed above are considered critical, for which there are not alternative suppliers and there is a risk of shortage in their territory, and therefore outside the scope of the non-complianace statement.

2019-07-30

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

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