Agencia Española de Medicamentos y Productos Sanitarios

Report No: ***INS/GMP/2016/020-021_PE0101228/PE0101232***

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. (YANTOU CAMPUS)***
Site address: ***56 Binhai Road, Jiaojiang District, taizhou City, Zhejiang province, Taizhou, Zheijiang, 318000, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-06-04*** , 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 (NCR) applies to all active pharmaceutical ingredients, intermediate products and medicinal products manufactured in the three campuses (Waisha Campus, Yantou Campus and East Factory Campus) of the site. The list of active ingredients (list maybe non-exhaustive) as provided by the company: Acarbose, abamectin, aripripazole, cytarabine, atorvastatin calcium, ansamitocin, bicalutamide, eprinomectin, spinosad, doramectin, dactinomycin, fludarabine phosphate, fluvastatin sodium, quetiapine fumarate, cyclophosphamide, cycloserine, metothrexate, tylosin tartrate, granulated tylosin concentrate, tylan G250, vinorelbine tartrate, capreomycin sulphate concentrate, capecitabine, cladribine, letrozole, linezolid, bleomycin sulphate, kanamycin sulfate acid, lovastatin, losartan potassium, mesna, milbemycin oxime, micafungin sodium, pitavastatincalcium, pravastatin, pravastatin sodium, celecoxib, selamectin, sulbactam sodium, mitomycin, tazobactam, tigecycline...

Part 3

1. Nature of non-compliance:

Overall 57 deficiencies were observed during the inspection, 3 critical and 17 major.[Critical 1] The cross-contamination risk was not fully identified and mitigated. Fipronil API (ectoparasiticide for external application to animal) was produced in the same building, same areas and same equipment than another active ingredient (Clorsulon) and in the same building and same area than Praziquantel. Fipronil was stored in the same room in warehouse than other active ingredients for human use and veterinary use. HVAC systems, dust extraction systems and cleaning validation were not adequate. Additionally, there were three Penem intermediates stored in the cold storage room located in warehouse Y05. The material was sampled in the same sampling room as other solid materials. [Critical 2] The three Fipronil API intermediates were not manufactured at Hisun Pharmaceutical site. In Site Master File and other documents it is falsely stated that the manufacture of the three intermediates took place at Zhejiang Hisun Pharmaceutical Site. [Critical 3] Bad documentation practice and deficient material management, specifically, uncontrolled documents were found in a warehouse intended for other purposes and uncontrolled packaging materials bearing variable data as batch number and expire date were found in a warehouse intended for other purposes. [Major deficiencies] The 17 major deficiencies observed were identified in the areas of quality pharmaceutical system and senior management responsibilities, cleaning validation, medicinal product identification, filter usage and maintenance, deviations and re-testing of stability studies, computerised system validation, audit trail of computerised systems, document control, raw material dispensing, handling of expired products, material sterilization, intermediate holding times, nitrogen and compressed air testing frequency, vent filter integrity testing, reference standards used for testing and non-accurate information provided in Site Master File.

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. 2. The submission of a variation application for introducing alternative manufacturers of active ingredients, intermediate products and finished products is recommended.

Recall of batches already released

No recall of the active ingredients, intermediate products and finished products 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 measures B1 and B2, these results should be communicated by MAH to NCA. The decision to be made by NCA, following an assessment between the NCA and MAHs, 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.

Prohibition of supply
Prohibition of supply 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, current valid GMP certificates should be withdrawn. The following additional measures are recommended: A. Due to the number and severity of the findings detected, current valid GMP certificates should be withdrawn. B.1. 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, including impurities, residual solvents and microbial burden. This measure is not applicable for batches that are currently on the market. B.2. To oblige European manufacturers and/or importers to perform full analytical testing of every batch of intermediate products and finished products sourced from Zhejiang Hisun or containing APIs or intermediates sourced from Hisun, including impurities, residual solvents and microbial burden. This measure is not applicable for batches that are currently on the market.

Additional comments
Due to their nature, the observed deficiencies are considered to apply to all active substances, intermediate products and medicinal products manufactured at the three campuses of Zhejiang Hisun Pharmaceutical, Co., Ltd. site (Waisha Campus, Yantou Campus and East Factory Campus). The inspection findings have a potential to impact on all the active ingredients, intermediate products and finished products manufactured in the site. Marketing authorisation holders are requested to contact the relevant National Competent Authority to verify whether their products 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-compliance statement.

2016-09-19

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

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