檔　　號：
保存年限：

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受文者：中華民國西藥代理商業同業公會

發文日期：中華民國105年12月6日
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速別：普通件
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊(A21020000I105110668501-1.pdf、A21020000I105110668501-2.pdf、A21020000I105110668501-3.pdf)

主旨：有關中國原料藥廠「Zhejiang Hisun Pharmaceutical Co., Ltd」共3個廠區經國際通報嚴重違反GMP乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、西班牙衛生主管機關Spanish Agency of Medicines and Medical Devices（AEMPS）於105年6月4日查核旨揭原料藥廠，判定嚴重違反GMP，並於105年9月19日發布「STATEMENT OF NON COMPLIANCE WITH GMP」（詳如附件）。

二、承上，西班牙AEMPS已啟動相關後續處置，包括：

(一)對於使用旨揭藥廠所生產原料藥之藥品許可證新查登或變更申請案，應不予許可。

(二)建議使用旨揭藥廠之原料藥生產中間製品（Intermediate products）及最終製劑產品（Finished products）之製劑廠，應考慮變更原料藥製造廠。

(三)目前雖尚未針對旨揭藥廠生產之原料藥、中間製品及最終製劑產品啟動回收。但對於使用旨揭藥廠原料藥之製

劑廠，應對廠內庫存之原料藥及最終產品，執行全項檢驗，檢驗項目應包括不純物、殘留溶劑及微生物限量，以評估相關產品是否啟動回收、是否有其他可替代之原料來源與缺藥疑慮。

(四)除非無可替代之原料來源或有缺藥疑慮之情況，嚴重違反GMP狀態尚未解除前，相關原料藥應暫停出貨。

(五)歐盟國家原核發給旨揭藥廠之相關GMP證明文件皆已廢止。

三、另，歐洲EDQM亦於105年10月10日凍結（SUSPEND）旨揭工廠之CERTIFICATE OF SUITABILITY（CEP）品質證明文件2年，待通過GMP複查後，始得恢復。

四、鑑於旨揭原料藥之製造品質無法符合GMP之要求，可能對藥品製造品質帶來影響與危害，請轉知所屬會員釐清相關輸台製劑產品是否使用旨揭原料藥廠所生產原料藥，並應依說明段二所述辦理。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、中華民國藥品行銷暨管理協會

副本：電2016-12-06 09:38:20

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. (Waisha Campus)***
Site address: ***46 Waisha Road Jiaojiang District, Taizhou City, Zhejiang, 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)

Manufacture of active substance. Names of substances subject to non-compliant :
CLORSULON(en)
PRAZIQUANTEL(en)
FIPRONIL(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : CLORSULON	
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 : Drying and milling
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Drying and 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
Active Substance : PRAZIQUANTEL	
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 : Drying and milling
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Drying and 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

Active Substance : FIPRONIL

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates *Special Requirements:* 6. Ectoparasiticides 3.1.2 Manufacture of crude active substance *Special Requirements:* 6. Ectoparasiticides 3.1.3 Salt formation / Purification steps : Drying and milling *Special Requirements:* 6. Ectoparasiticides
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Drying and milling *Special Requirements:* 6. Ectoparasiticides 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) *Special Requirements:* 6. Ectoparasiticides 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) *Special Requirements:* 6. Ectoparasiticides
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing *Special Requirements:* 6. Ectoparasiticides 3.6.2 Microbiological testing excluding sterility testing *Special Requirements:* 6. Ectoparasiticides

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). The list of active ingredients (list maybe non-exhaustive) as provided by the

company: doxorubicin hydrochloride, epirubicin hydrochloride, vinorelbine tartrate, vincristine sulphate, mycophenolate mofetil, tacrolimus, dactinomycin, paclitaxel, bleomycin sulfate.

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

Confidential
Spanish Agency of Medicines and Medical Devices
Tel: *Confidential*
Fax: *Confidential*

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, sulbactant 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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Spanish Agency of Medicines and Medical Devices
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Spanish Agency of Medicines and Medical Devices

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

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 ***2016-06-04*** , it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/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

Human Medicinal Products

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;	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.1 Capsules, hard shell 1.2.1.13 Tablets
1.5	**Packaging**
	1.5.1 Primary Packing 1.5.1.1 Capsules, hard shell 1.5.1.13 Tablets
1.6	**Quality control testing**
	1.6.2 Microbiological: non-sterility *1.6.3 Chemical/Physical*

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).

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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