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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警訊乙份(A21020000I105110216600-1.pdf)

主旨：有關PIC/S 警訊平台（PIC/S Rapid Alert System）通報中國原料藥廠「Chengdu Okay Pharmaceutical Co., Ltd.」(廠址：No.15 Chuangye Road Linqiong Industrial Zone, Qionglai, Sichuan Province, P.R.China）嚴重違反GMP乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、波蘭衛生主管機關MAIN PHARMACEUTICAL INSPECTORATE（MPI）併同歐洲理事會European Directorate for the Quality of Medicines & Healthcare（EDQM）查核旨揭原料藥廠，判定違反GMP，並於105年2月19日發布「STATEMENT OF NON-COMPLIANCE WITH GMP」，受影響原料藥品項為「Diosmin」（詳如附件）。

二、承上，波蘭MPI建議使用該原料之製劑廠應針對旨揭原料藥廠之原料藥進行完整全項檢驗以評估是否啟動相關產品回收，確保品質無虞。

三、另，歐洲EDQM亦於105年4月11日凍結（Suspend）旨揭工廠「Diosmin」之品質證明（the Certificate of Suitabi

lity RO-CEP 2012-359-Rev 01）2年及暫停其他CEP申請案，待再次通過GMP複查後，始得恢復。

四、鑒於旨揭原料藥廠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：中華民國藥品行銷暨管理協會、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

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The Main Pharmaceutical Inspectorate

Report No: *GIF-IW-400/0493_01_01/04/36-1/16*

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 Poland confirms the following:
The manufacturer: ***Chengdu Okay Pharmaceutical Co. Ltd.***
Site address: ***No. 15 Chuangye Road Linqiong Industrial Zone, Qionglai, Sichuan Province, 611530, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-10-28*** , 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 substance(en)

Manufacture of active substance. Names of substances subject to non-compliant :
DIOSMIN(en) / DIOSMINA(pl)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : DIOSMIN	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : crystallization
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, pulverization, blending 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

Part 3

1. Nature of non-compliance:
Overall, 21 deficiencies were observed during the inspection, including 5 critical and 10 major deficiencies. The critical deficiencies were observed in QC Dept. including calculation of impurities of Diosmin and there were no records of standard (used as a reference) for testing in-house standard. Also the data integrity was not guaranteed. In manufacturing Dept. presented measuring methods were inadequate to the results. The condition in clean area was not acceptable for final product. Critical deficiences: Testing of the final product: There was incorrectly way of calculation the impurities and Diosmin content. There were no records of prepared in-house HPLC standard. There was no confirmation of the conditions HPLC analysis. Computerized systems - documentation and control: There was found in HPLC system that the method was changed, without any savings of previous method. There were no logins and passwords to the HPLC system and no procedure for granting permission to access to the HPLC system. There was no register of persons autorized to access to to the HPLC system. On the same computer station there were two different HPLC software. Manufacturing documentation: Presented measuring methods of pH during the inspection time were inadequate to the results recorded in the batch report. Premises: Crude Diosmin drying was carried out in an area which did not provide the appriopriate coditions during the discharge from the dryer. Qualification of equipment: Some data of HVAC system qualification had been falsified. The major deficiencies were observed among others: in the warehouse, in the manufacturing documentation and in the production area.
Action taken/proposed by the NCA **Recall of batches already released** It is recommended to perform a comlete analysis of the substance by manufacturer of medicinal products.
Additional comments The inspection was performed by reques of API importer.

2016-02-19

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

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