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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(A21020000I105110215200-1.pdf)

主旨：PIC/S警訊平台（PIC/S Rapid Alert System）通報印度原料藥廠「Dhanuka Laboratories Ltd.」(廠址：7 km, Old Manesar Road, Village Mohammedpur, Gurgaon, Haryana, 122 001, India）嚴重違反GMP乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、克羅埃西亞衛生主管機關Agency for Medicinal Products and Medical Devices of Croatia（HALMED）於105年2月19日查核旨揭原料藥廠，判定嚴重違反GMP，並於105年5月23日發布「STATEMENT OF NON-COMPLIANCE WITH GMP」，受影響之原料藥品項包括「Cefixime」等共計14項。（詳如附件）

二、承上，克羅埃西亞HALMED已啟動相關後續處置，包括：

(一)建請波蘭官方廢止原核發之GMP證明文件（GIF-IW-N-4022/161/13），經查，該GMP證明文件業已廢止。

(二)使用旨揭原料藥廠原料藥之製劑產品，應考慮變更原料來源。

(三)GMP狀態未改善完畢前，原料藥暫停出貨。

三、另，歐洲EDQM亦於105年4月8日凍結（Suspend）旨揭工廠「Cefixime」與「Cefuroxime axetil」相關品質證明CEP（the Certificate of Suitability）2年及不准「Cefixime Process 2」與「Cefpodoxime proxetil」之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

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Agency for Medicinal Products and Medical Devices of Croatia

Report No: *UP/I-530-10/16-06/03, 381-13-04/151-16-04*

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 Croatia confirms the following:
The manufacturer: ***Dhanuka Laboratories Ltd.***
Site address: ***7 km, Old Manesar Road, Village Mohammedpur, Gurgaon, Haryana, 122 001, India***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-02-19*** , 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 substances(en)

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

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : CEFIXIME	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates *Special Requirements:* 1. B-lactam antibiotics 3.1.2 Manufacture of crude active substance *Special Requirements:* 1. B-lactam antibiotics 3.1.3 Salt formation / Purification steps : crystallisation *Special Requirements:* 1. B-lactam antibiotics
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, milling, blending *Special Requirements:* 1. B-lactam antibiotics 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) *Special Requirements:* 1. B-lactam antibiotics 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:* 1. B-lactam antibiotics
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing *Special Requirements:* 1. B-lactam antibiotics 3.6.2 Microbiological testing excluding sterility testing

4. Non-Compliant Other Activities - Active Substances :
Other active substances and intermediates manufactured on the site were not in the scope of the inspection: Cefuroxime axetil, Cefuroxime Acid, Cefdinir, Cefpodoxime Proxetil,Cefpodoxime Acid,Cefaclor, Cefditoren Pivoxil, Cefditoren Sodium, Cefprozil EP/USP, Cefixim Process2, 7-APCA,7-AVCA,7-ACCA However, critical finding was discovered in the QA system.

Part 3

1. Nature of non-compliance:

This inspection was performed in the framework of the CEP dossier for the manufacture of Cefixime R1-CEP 2003-014-Rev 02. The inspection identified in total 32 deficiencies against EU GMP. One of them was categorized as critical and related to the Company`s weak Quality Assurance System. Seven deficiencies were categorized as major deficiencies and were related to: Quality Assurance (2), Buildings and facilities, Documentation, Materials Management/Storage, Laboratory controls, Qualification. [Critical] The QA system implemented on site, which related to the workshops that were engaged in the manufacture of Cefixime, was found to be weak and not capable of proper design, planning, implementation, maintenance and continuous improvement of a system that allows the consistent delivery of products with appropriate quality attributes. These observations are accordingly identified in the relevant sections. The GMP violations were considered as very severe and thus bearing a risk to either human or veterinary patients. [Major] Due to a lack of control, a mix-up of CEP-grade batches of Cefixime with those derived by a different process – and their subsequent supply to EU customers – could not be excluded. [Major] No release of individual batches took place at the time of the inspection. That means that the requirements, such as batch production and batch analytical report review(s) were not conducted and the batches were further used for blending after testing. [Major] A centrifugation area on the basement of the intermediate building, the rooms hosting the fluid bed dryers as well as the dryers themselves were found as not in accordance with the requirements because a contamination of the products openly handled in this area could not be excluded. [Major] Batch Production Records, Equipment Cleaning Records and Lot Making Production Records (BPR, ECR, LMPR) were issued by printing the relevant document from a pdf-file. Core principles of the management of electronic documentation was found not considered (or disregarded) [Major] Several observations with regard to the receipt, storage and dispensing of raw materials, key starting materials, intermediates and finished APIs were made and leading to the conclusion that a negative impact of the quality cannot be excluded. [Major] Severe violations to EU GMP were made with regard to the IPC laboratory and the analytical operations conducted in this lab. [Major] Out of a list of 62 instruments (SMF), only four were fully qualified. A further five instruments had undergone only DQ, IQ and OQ steps NB: It must also be noted that the previous EDQM inspection categorized observations related to the qualification of equipment as a major deficiency. The Company failed to implement the CAPA in a holistic way as it addressed only the equipment in question.

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. GIF-IW-N-4022/161/13
Withdrawal of current EU GMP certificate issued by The Main Pharmaceutical Inspectorate, Poland (GIF-IW-N-4022/161/13).

Requested Variation of the marketing authorisation(s)
Removal from marketing authorizations should be considered.

Prohibition of supply
No further batches to be supplied to the market whilst this statement remains in force.

Suspension or voiding of CEP (action to be taken by EDQM)
Suspension of R1-CEP 2003-014-Rev 02 Cefixime R0-CEP 2011-173-Rev 00 Cefuroxime axetil has been decided by EDQM's AdHoc Committee.

2016-05-23

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

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Agency for Medicinal Products and Medical Devices of Croatia
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