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保存年限：

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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(A21020000I105110324900-1.pdf)

主旨：有關中國原料藥廠「Dongying Tiandong Pharmaceutical Co., Ltd.」(廠址：No.1236, Nan-er Road China-257067 Dongying City, Shandong Province) 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、法國衛生主管機關French National Agency for Medicines and Health Products Safety (ANSM) 於104年12月7-9日查核旨揭原料藥廠，判定嚴重違反GMP，並於105年2月25日發布「STATEMENT OF NON COMPLIANCE WITH GMP」，受影響之原料藥包括「Enoxaparin Sodium」及「Heparin Sodium」共2項。(詳如附件)

二、承上，法國ANSM已啟動相關後續處置，包括：

(一)建請廢止波蘭官方核發之EU GMP證明文件 (GIF-IW-N-4022/68/13)；經查，該GMP證明文件業已廢止。

(二)基於風險管理 (Quality Risk Management) 原則，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)基於風險管理原則，使用相關原料藥之製劑產品許可證持有者應評估是否啟動回收。

(四)GMP狀態尚未改善完畢前，原料藥暫停出貨。

三、另，歐洲EDQM亦於105年4月18日凍結（SUSPEND）旨揭工廠「Enoxaparin Sodium」相關品質證明CEP（the Certificate of Suitability）2年，待通過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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French National Agency for Medicines and Health Products Safety

Report No: *15MPP066NCS*

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 France confirms the following:
The manufacturer: ***Dongying Tiandong Pharmaceutical Co., Ltd.***
Site address: ***No. 1236, Nan-er Road, Dongying City, Shandong Provice, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-12-09*** , 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;	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.17 Other: active substance(en)

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

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : ENOXAPARIN SODIUM	
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 : Precipitation, filtration
3.2	**Extraction of Active Substance from Natural Sources**
	3.2.5 Modification of extracted substance Animal 3.2.6 Purification of extracted substance Animal
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Drying, milling, 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 3.6.4 Biological Testing
Active Substance : HEPARIN SODIUM	
3.2	**Extraction of Active Substance from Natural Sources**
	3.2.5 Modification of extracted substance Animal 3.2.6 Purification of extracted substance

	Animal
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Dryng, milling, 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 3.6.4 Biological Testing

Part 3

1. Nature of non-compliance:

Overall, 10 deficiencies were observed during the inspection, 2 Critical and 3 Major deficiencies: [Critical 1] PCR results of Crude Heparin showing the presence of ruminant DNA received from approved suppliers were manipulated. There was no evidence that the samples retested came from the same batch tested initially; [Critical 2] The quality system implemented by the company for ensuring the full traceability of crude Heparin was identified as very weak : e.g., the traceability from slaughterhouses/abattoirs was not available and not assessed during the audits of the suppliers (lack of supporting documents for the received lots) ; [Major 1] Misunderstanding of the basic GMP principles for handling of out of specification (OOS) results and deviations (e.g., 7 batches of crude Heparin received in 2014 and 2015 were obtained OOS for potency and used for the manufacturing of finished APIs without any OOS investigation); [Major 2] The evaluation of the new suppliers of crude Heparin was deficient: the procedure was not followed, no delivery documents were available, the testing was not systematically recorded in the equipment logbook, the samples from approved suppliers were contaminated during the sampling operation, etc. ; [Major 3] The assessment of 1 H NMR spectrum (Heparin Sodium) and 13 C NMR (Enoxaparin Sodium) used for identification test were deficient (e.g., the presence of an additional peak at the C13 NMR obtained by a subcontracted laboratory was not identified and investigated)

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. GIF-IW-N-4022/68/13
Using QRM principles, consideration of withdrawal of current valid EU GMP certificate issued by the Main Pharmaceutical Inspectorate of Poland (GIF-IW-N-4022/68/13).

Requested Variation of the marketing authorisation(s)
Using QRM principles, the removal of the site from MAs should be considered.

Recall of batches already released
Consideration of a recall of product should be given due to the critical findings observed. Using QRM principles, National supply situation and clinical requirements should be taken into account when making this decision.

Prohibition of supply
The site has been issued a statement of non compliance and should not be named on any marketing authorisations whilst this statement remains in place.

Suspension or voiding of CEP (action to be taken by EDQM)
Suspension of CEP 2005-258 (Enoxaparin sodium).

2016-02-25

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

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Confidential
French National Agency for Medicines and Health Products Safety
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