

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 manufacturer¹

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 Province, 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;

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| 1.2 | Non-sterile products |
| | <i>1.2.1 Non-sterile products (processing operations for the following dosage forms)</i> 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

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|------------|---|
| 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

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|------------|--|
| 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

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| 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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