Austrian Medicines and Medical Devices Agency

Report No: ***INS-482710-0001-008***

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 Austria confirms the following:
The manufacturer: ***QILU TIAHNE PHARMACEUTICAL CO LTD***
Site address: ***NO 849, DONGJIA TOWN, LICHENG DISTRICT, JINAN CITY, SHANDONG, CN-250105, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2018-08-09*** , 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
- 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

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;

1.1	**Sterile products**
	1.1.1 Aseptically prepared (processing operations for the following dosage forms) 1.1.1.2 Lyophilisates Special Requirements 1 B-lactam Antibiotics 1.1.1.6 Other: Powder filling(en) Special Requirements 1 B-lactam Antibiotics
1.4	**Other products or manufacturing activity**
	1.4.2 Sterilisation of active substance/ excipients/ finished product 1.4.2.1 Filtration Special Requirements 1 B-lactam Antibiotics
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility *1.6.2 Microbiological: non-sterility* *1.6.3 Chemical/Physical*

Manufacture of active substance. Names of substances subject to non-compliant :
TAZOBACTAM SODIUM(en)
TAZOBACTAM(en)
TAZOBACTUM SODIUM(en)
PIPERACILLIN SODIUM(en)
PIPERACILLIN(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance : TAZOBACTAM 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 : dissolution, reaction and adjusting
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps :

	filtration, loading, lyophilization, unloading, granulation, blending and filling into tins 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 3.6.3 Microbiological testing including sterility testing

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3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.2 Microbiological testing excluding sterility testing 3.6.3 Microbiological testing including sterility testing

Active Substance : PIPERACILLIN 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 : dissolution, reaction and adjusting
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : filtration, loading, lyophilization, unloading, granulation, blending and filling into tins 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 3.6.3 Microbiological testing including sterility testing

Active Substance : PIPERACILLIN

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 : dissolution, reaction and adjusting
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : filtration, loading, lyophilization, unloading, granulation, blending and filling into tins 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 3.6.3 Microbiological testing including sterility testing

Any restrictions related to the scope of this statement :

Building	Room	Line/equipment	QC testing	Products
workshop #4, #5 & #9; finished goods warehouse #22;				

Part 3

1. Nature of non-compliance:

In total, approximately 30 deficiencies were observed. Amongst them, several critical and major deficiencies were identified in the field of Quality Management, Environmental Monitoring, Cross Contamination Control and Cleaning. Production areas, Equipment, Cleaning processes, maintenance, storage, utilities and quality oversight are not suitable to manufacture products under GMP-conditions. The established cleaning procedure in the facility's weighing room (3-16) of workshop #5 is not suitable for the handling of highly potent substances to avoid cross-contamination. Triphosgene (a highly toxic raw material for production of Piperacillin) is stored there. In general, aseptic production processes do not comply with current EU-GMP regulations, e.g.: a) Environmental monitoring concept: I. Monitoring positions do not reflect worst case locations based on risk evaluation, e.g. movement of operators (locations of particle sensors and settle plates placed in corners, not covering operators movement) II. Environmental monitoring starts after clean-up phase III. The inspectors have determined that permanently installed active air sampling devices are present within the RABS system (cleanroom class A); this equipment is not in use during routine production b) Environmental monitoring procedure during production: I. Particle monitoring cleanroom class A is not performed continuously during the whole production process (to cover all operations) II. The tube length of mobile particle counters does not comply with current state of the art requirements (ISO 14644-1, -2) III. In cleanroom class A, permanently installed particle sensors are not appropriate for the particle size considered; e.g. the tube (bottle inlet after sterilization tunnel), shows multiple 90° bends and a length exceeding the state of the art requirements to avoid particle losses in the tubing. c) Interventions performed by operators: (observed in Workshop #9) I. Removal of discarded bottles II. Emptying the discard box III. Forwarding of stuck bottles on the conveyor belt d) Hygienic behavior of operators: (observed in Workshop #9) I. no exchange procedure of gloves during production II. distribution of solid material (powder) all over clean room class B area through operators boots by walking back and forth, e) Maintenance of equipment: (observed in Workshop #9) I. Screw (conveyor belt) dropped down on the floor during operation (this was not recognized by the operators, no actions were taken) Last but not least: Cleaning concept and procedures do not comply with EU-GMP regulations in the following: a) Cleaning concept of workshop #9 (aseptic filling line 2, FDF) lacks in a logical sequence of operation steps (e.g. starting of cleaning activities in cleanroom class A prior to removal of remaining filled bottles of product still present at the conveyor belt; removal of discard box filled with un-stoppered bottles containing powder after starting of cleaning RABS (cleanroom class A) b) General procedures such as re-using cloths in clean room class A c) Surface cleaning of cleanroom class B is not effectively performed (no exchanging of mop-heads in a regular interval) d) Mix-up of cleaning activities in cleanroom class A and B e) Operators are not effectively trained on how to perform cleaning activities (lack of detailed cleaning instructions in respective SOPs) Listing stopped due to 4000 char. restriction. Details available on request. Considering the CAPA-Plan provided by the company one critical deficiency was solved, the others were reclassified to "major". Due to the severeness of the deficiencies an on-site re-inspection is deemed necessary.

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. IT/E/GMP/API/09/2016
Several other current valid Cerificates (e.g. DE_RP_01_GMP_2018_0002) seem to be affected as well. The withdrawal of the certificates mentioned was discussed with the respective issuing Authorities.

Additional comments
1) EMA will organise a multinational inspection early 2019 (AT/DE/IT/FR) 2) Proposal to avoid product shortages until next positive inspection outcome: 2.1) A designated (qualified) person of the national manufacturer has to be present on site during production of all subsequent batches to engage GMP-compliance 2.2) Existing and subsequent batches have to undergo extensive retesting (unknown impurities, sterility based on a confirmed statistical scheme)

Teleconference Date	2018-11-08	**Teleconference Time (CET)**		**Dial in no.**	

2018-11-26

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

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Austrian Medicines and Medical Devices Agency
Tel: ***Confidential***
Fax: ***Confidential***