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Italian Medicines Agency

Report No:***IT/NCR/API/01/2023***

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 Italy confirms the following:

The manufacturer: **Istituto Biochimico Italiano Giovanni Lorenzini S.p.A.**

Site address: **Via Fossignano 2, Aprilia, 04011, Italy**

OMS Organisation Id. / OMS Location Id.: **ORG-100001469** / **LOC-100005026**

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2023-05-30***, 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

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(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
1.4 Other products or manufacturing activity
1.4.1 Manufacture of 1.4.1.3 Other: active substances(en)

Manufacture of active substance. Names of substances subject to non-compliant:
[00000000002155] POTASSIUM CLAVULANATE STERILE(en)
[00000000004411] TAZOBACTAM SODIUM STERILE(en)
[0000000000370] AMOXICILLIN SODIUM STERILE(en)
[00000000001798] FLUCLOXACILLIN SODIUM STERILE(en)
[00000000003117] PIPERACILLIN SODIUM STERILE(en)
[0000000000379] AMPICILLIN SODIUM STERILE(en)
[00000000004401] SULBACTAM SODIUM STERILE(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance:POTASSIUM CLAVULANATE STERILE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Salt formation, crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: Drying 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 3.6.3 Microbiological testing including sterility testing 3.6.4 Biological Testing
Active Substance:TAZOBACTAM SODIUM STERILE	

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Dissolution/Salt formation Special Requirements: 1.B-lactam antibiotics
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: Lyophilisation
3.6	**Quality Control Testing**
	3.6.4 Biological Testing 3.6.3 Microbiological testing including sterility testing 3.6.1 Physical / Chemical testing

Active Substance:AMOXICILLIN SODIUM STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Salt formation, crystallisation Special Requirements: 1.B-lactam antibiotics
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: Drying, sieving 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 3.6.3 Microbiological testing including sterility testing 3.6.4 Biological Testing

Active Substance:FLUCLOXACILLIN SODIUM STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Crystallisation Special Requirements: 1.B-lactam antibiotics
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: Drying, sieving
3.6	**Quality Control Testing**
	3.6.4 Biological Testing 3.6.3 Microbiological testing including sterility testing 3.6.1 Physical / Chemical testing

Active Substance:PIPERACILLIN SODIUM STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Salt formation/Salt formation, crystallisation Special Requirements: 1.B-lactam antibiotics
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: Lyophilization/Drying, sieving
3.6	**Quality Control Testing**
	3.6.4 Biological Testing 3.6.3 Microbiological testing including sterility testing

	3.6.1 Physical / Chemical testing

Active Substance:AMPICILLIN SODIUM STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Salt formation, crystallisation Special Requirements: 1.B-lactam antibiotics
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: Drying, sieving
3.6	**Quality Control Testing**
	3.6.4 Biological Testing 3.6.3 Microbiological testing including sterility testing 3.6.1 Physical / Chemical testing

Active Substance:SULBACTAM SODIUM STERILE

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Crystallisation Special Requirements: 1.B-lactam antibiotics
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	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) 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.1 Physical processing steps: Drying, sieving
3.6	**Quality Control Testing**
	3.6.4 Biological Testing 3.6.3 Microbiological testing including sterility testing 3.6.1 Physical / Chemical testing

4. Non-Compliant Other Activities - Active Substances:
SULBACTAM SODIUM (Confidential); TAZOBACTAM (Confidential) AMPICILLINA (Confidential) FLUCLOXACILLIN SODIIUM (Confidential) PIPERACILLIN (Confidential) SULBACTAM (Confidential) TERT-BUTYL AMINO CLAVULANATE(Confidential)

Clarifying remarks (for public users):
NA

Part 3

Nature of non-compliance: During the inspection, 18 deficiencies were found, 1 classified as "Critical" ad 8 classified as "Major" mainly in the following areas: Sterility assurance (3), Premises: material flow in the clean areas (1), Qualifications/validation of classified areas (1), Deviations and OOS management (3), Product Quality Review management (1). Critical deficiency and four out of eight major deficiencies are mainly referring to the aseptic production which constitutes a critical risk for public health due to the lack of sterility assurance of the drug substances. The observed deficiencies are related mainly to the sterile active substances manufactured from June 2021 to March 2022 at the site but all the sterile APIs manufactured in the site may be potentially impacted by the findings. CAPA evaluation is still on going.

Action taken/proposed by the NCA:

Withdrawal, of current valid GMP certificate No. IT-API/45/H/2021
Withdrawal of current valid GMP certificate GMPAPI N°: IT-API/77/H/2022 issued date 2022/04/06. AIFA suspended the authorisation N° API - 24/2022, issued date 2022/04/06, related the manufacturing of sterile active substances and import of APIs internally processed for the production of sterile active substances.

Recall of batches already released
A final statement of non compliance will be issued for all manufactured sterile APIs. At the moment recall from the market was not put in place. Each involved NCA should evaluate following assessment conducted in conjunction with MAHs if a recall of medicinal product is needed. Medicinal products containing the active substances manufactured by IBI are considered critical; shortage of the medicinal products is considered a real risk.

Prohibition of supply
Evaluation should take into account if there are alternative suppliers and potential risk of shortage. Company retested for sterility and endotoxins the APIs batches manufactured at the time of the AIFA inspection but not used yet for finished products manufacture. The re-test results of these batches confirmed the release analytical results, therefore after the evaluation of the impact of the findings during the inspection and the re-test results, on 28 July 2023, the Company asked for the authorisation for the internal release of the batches. AIFA evaluation is on going.

Suspension or voiding of CEP (action to be taken by EDQM)
The active substance Amoxicillin sodium Sterile is covered by CEP 1996-013 The active substance Ampicillin sodium sterile is covered by : CEP 1999-169 The active substance Flucloxacillin sodium Sterile is covered by CEP 1999-039 The active substance Piperacillin sodium Sterile is covered by CEP 1999-117 and CEP 2006-252 The CEP list may not be exhaustive

Others
The company holds the authorization for manufacturing sterile APIs and registration for non-sterile APIs import. Proposed actions: 1)authorization for manufacturing sterile APIs to be suspended; 2) registration for import of non-sterile APIs used such as for the production of medicinal products to be maintained as the statement of non compliance does not impact on this activity. This manufacturer for aseptic sterile active substance production should not be approved in any new/ongoing applications until appropriate corrective action will be implemented and GMP compliance will be resumed.

Teleconference Date:	Teleconference Time (CET):	Dial in no.:

2023-08-04 Name and signature of the authorised person of the Competent Authority ofItaly

Confidential

Italian Medicines Agency

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