*Spanish Agency Of Medicines And Medical Devices*

Report No: ***PE010-4837***

# 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 Spain confirms the following:
The manufacturer: ***Ceph Lifesciences Private Limited***
Site address: ***Unit II Village Saidpura, Sahibzada Ajit Singh Nagar, Derabassi, S.A.S Nagar, Punjab, 140507, India***
OMS Organisation Id. / OMS Location Id.: ***ORG-100056505*** / ***LOC-100101295***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2025-02-11***, 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 and an appropriate level of GMP as referred to in Article 46(f) of Directive 2001/83/EC.

Note to receiving authorities: Please contact the issuing authority within 20 working days in case there are critical(2) medicinal products potentially affected by this statement.
Manufacturing Authorisation Holders directly affected by this statement have failed to comply with their obligations under Art. 46 of Directive 2001/83/EC or Art. 93(1)(j) to (l) of Regulation (EU) 2019/6 and as a consequence the Qualified Person referred to in Art. 48 of Directive 2001/83/EC and Art. 97(1) of Regulation (EU) 2019/6 is unable to perform the batch certification referred to in Art. 51 of Directive 2001/83/EC and Art. 97 (6) and (7) of Regulation (EU) 2019/6.
In exceptional circumstances there may be no objection to the Qualified Person certifying affected batches thereby allowing their release provided all of the following conditions are fulfilled:

1. Batch certification is performed in order to maintain supply of critical medicinal products only.
2. A documented risk assessment has been performed by, or on behalf of, the Qualified Person and additional actions have been implemented by the manufacturing and/or batch release site to mitigate the risks posed by the non-compliance. Note: Repeated testing alone is not normally sufficient risk mitigation but, together with other actions, can form part of a strategy commensurate with the nature and the level of risk.
3. A thorough risk-benefit evaluation has been performed for the acceptance of risk and a report prepared that takes full account of the nature of the non-compliance with the involvement of:
   - The Manufacturing Authorisation Holder and the Qualified Person of the site responsible for batch certification.

- The manufacturing site subject to this Statement of Non-Compliance, if different from the above.
- The relevant Marketing Authorisation Holder(s).

The report has been shared with the National Competent Authorities of the countries in which distribution of the affected batches is anticipated and that any comments from those authorities have been taken into account.

4. Written confirmation has been obtained from the National Competent Authorities in whose territories the affected batches are intended to be distributed that the product is considered critical on its territory, and that there is no objection to distribution.
5. The Supervisory Authority has been informed, if different from the above, and it has not suspended or revoked the relevant Manufacturing Authorisation.
6. The affected Marketing Authorisations have not been revoked or suspended.
7. Any further conditions imposed by the Supervisory Authority and other involved National Competent Authorities are met.

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[1] *The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and Art. 94(2) of Regulation (EU) 2019/6, as amended, is also applicable to importers.*

[2] *See Appendix 3 of the relevant procedure in the Compilation of Union Procedures.*

## 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;

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

Manufacture of active substance. Names of substances subject to non-compliant:
***CEFUROXIME AXETIL(en)***
***CEFTRIAXONE SODIUM(en)***
***CEFUROXIME SODIUM(en)***
***CEFOTAXIME SODIUM(en)***
***CEFIXIME(en)***
***CEFEPIME DIHYDROCHLORIDE MONOHYDRATE(en)***
***CEFPODOXIME PROXETIL(en)***
***CEFTAZIDIME PENTAHYDRATE(en)***
***CEFAZOLIN SODIUM(en)***
***CEFEPIME(en)***
***CEFEPIME HYDROCHLORIDE(en)***
***CEFTAZIDIME(en)***
***CEFOXITIN SODIUM(en)***
***CEFDINIR(en)***
***CEFDITOREN PIVOXIL(en)***
***CEPHALOTIN SODIUM(en)***
***CEPHALOTIN(en)***
***CEFTIBUTEN DIHYDRATE(en)***

## 3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance:CEFUROXIME AXETIL

| 3.1 | Manufacture of Active Substance by Chemical Synthesis |
|---|---|
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |

Active Substance:CEFUROXIME SODIUM

| 3.1 | Manufacture of Active Substance by Chemical Synthesis |
|---|---|
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps: |

| | |
|---|---|
| | crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFTRIAXONE SODIUM

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFOTAXIME SODIUM

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFIXIME

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |

Active Substance:CEFEPIME DIHYDROCHLORIDE MONOHYDRATE

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFPODOXIME PROXETIL

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |

Active Substance:CEFTAZIDIME PENTAHYDRATE

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFAZOLIN SODIUM

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFEPIME

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFEPIME HYDROCHLORIDE

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance |

| | |
|---|---|
| | 3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFTAZIDIME

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFOXITIN SODIUM

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFDINIR

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |

Active Substance:CEFDITOREN PIVOXIL

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |

Active Substance:CEPHALOTIN SODIUM

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEPHALOTIN

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |
| **3.4** | **Manufacture of sterile Active Substance** |
| | 3.4.1 Aseptically prepared |

Active Substance:CEFTIBUTEN DIHYDRATE

| | |
|---|---|
| **3.1** | **Manufacture of Active Substance by Chemical Synthesis** |
| | 3.1.1 Manufacture of active substance intermediates<br>3.1.2 Manufacture of crude active substance<br>3.1.3 Salt formation / Purification steps:<br>crystallization, centrifuging, drying, milling, sifting, micronization, homogenization and blending |

**Part 3**

**1.Nature of non-compliance:**

During inspection, 28 deficiencies were identified, 4 of them has been classified as critical and 3 as major. The critical deficiencies are related to Quality Assurance management, aseptic operations in relation to compliance with Annex I of the GMP, maintenance and cleaning of equipment and facilities, and computerised systems. And the major deficiencies were observed in the areas to validation of analytical methods, staff training and batch release. Since the deficiencies found transversally affect both the manufacturing of non-sterile APIs (some of whose manufacturing facilities were also inspected) as well as sterile API facilities, it has been decided to issue an statement of Non-compliance with GMP that affects both types of products. The most relevant or critical deficiencies observed during the inspection are described below : - A number of severe violations of EU GMP Part II, EU GMP Annex 1 and Annex 11, potentially posing a risk to the quality of manufactured products and therefore to public health, demonstrated a lack of Quality Assurance oversight and understanding of core requirements. Significant shortcomings were observed across the GMP spectrum, documented as part of this inspection such as sterility assurance of APIs, cross contamination control, maintenance of facilities and equipment, computerised systems and training. - The company failed to implement core principles of EU GMP Annex 1 “Manufacture of Sterile Medicinal Products”. Consequently, the sterility of the Active Pharmaceutical Ingredients (API) manufactured in Block SE, Nectar Life Science Unit II, cannot be guaranteed, posing a risk to human and/or veterinary health. Abundant and important shortcomings were found among the site related to but not limited to site design, materials management, personnel behavior in aseptic areas, quality of exposed surfaces and failure to identify applicable requirements, risks and risk mitigation measures regarding revised Annex and general GMP requirements. -There is a significant risk of contamination/cross contamination of non-sterile APIs/intermediates manufactured based on the cleaning and/or maintenance status of the facility and the equipment used. Several observations made during the inspection of Oral Block F conclude that the manufacturing facilities and equipment for active ingredients have not been adequately maintained over the years, resulting in a significant deterioration of their condition and therefore posing a risk to the quality of APIs and ultimately to the patient. These observations include lack of maintenance, cleaning, presence of corrosion, concrete cracks, signs of liquid leakages, lack of hand-washing facilities, and other significant signs of poor maintenance, management and hygiene. - Several potential breaches on data integrity were found. Main aspects related to computerised systems were not addressed. The firm failed to implement basic requirements with regard to computerised systems as outlined in EU GMP Annex 11 and EU GMP Part II section 5.4ff. The flaws detected could potentially lead to failures in analytical testing and/or breaches in data integrity. The following shortcomings, among others, were observed: outdated operating systems on HPLC systems (Windows XP, Windows 7), no traceability (e.g. audit trail) or approval of the change of some HPLC sequences, problems with operators’ privileges and lack of computerised systems validation. - The Company also disregards pivotal aspects of GMP rules such as training (for instance, on the reviewed Annex I or failure to fulfill training requirements of the personnel), analytical method validation (not even planned to be done), or batch release verifications.

**Action taken/proposed by the NCA**

**Requested Variationof the marketing authorisation(s)**

This manufacturer should not be authorised in any new/ongoing marketing authorization or variation applications for the active pharmaceutical ingredients as long as the non-compliance statement is in force. The submission of a variation application for introducing alternative manufacturers of the active substances is recommended.

**Recall of batches already released**

The need of recall of released batches of finished products where APIs manufactured on this site have been used should be assessed by each NCA but based on the information gained during the inspection there is no cause to recommend a recall of concrete batches.

**Prohibition of supply**

Due to the nature of the non-compliance, prohibition of supply is recommended, unless there are no alternative suppliers or there is a risk of shortage.

**Suspension or voiding of CEP (action to be taken by EDQM)**

The EDQM Ad Hoc Committee has suspended all affected CEP manufactured in these facilities: a. CEP 2009-045, Cefuroxime axetil, amorphous b. CEP 2010-342, Ceftriaxone sodium, sterile c. CEP 2011-062, Cefuroxime sodium,

sterile d. CEP 2011-226, Cefotaxime sodium, sterile e. CEP 2011-239, Cefixime f. CEP 2012-242, Cefepime dihydrochloride monohydrate, sterile g. CEP 2015-354, Cefpodoxime proxetil h. CEP 2016-170, Cefuroxime axetil, amorphous, Process-II i. CEP 2017-042, Cefixime, Process II j. CEP 2019-231, Ceftazidime pentahydrate with sodium carbonate for injection, sterile.

**Additional comments**

Substances (APIs) affected are listed below: 1. Substances covered by CEP(s) or CEP application(s): a. CEP 2009-045, Cefuroxime axetil, amorphous b. CEP 2010-342, Ceftriaxone sodium, sterile c. CEP 2011-062, Cefuroxime sodium, sterile d. CEP 2011-226, Cefotaxime sodium, sterile e. CEP 2011-239, Cefixime f. CEP 2012-242, Cefepime dihydrochloride monohydrate, sterile g. CEP 2015-354, Cefpodoxime proxetil h. CEP 2016-170, Cefuroxime axetil, amorphous, Process-II i. CEP 2017-042, Cefixime, Process II a.j. CEP 2019-231, Ceftazidime pentahydrate with sodium carbonate for injection, sterile. 2. Other substances (not covered by CEP applications): Cefazolin sodium Sterile, Cefepime for Injection Sterile, Cefepime Hydrochloride Sterile, Ceftazidime for injection Sterile, Cefoxitin Sodium Sterile, Cephalotin Sodium Sterile, Cephalotin for Injection Sterile, Cefdinir, Cefuroxime axetil Coated, Cefuroxime axetil Crystalline, Cefditoren Pivoxil Amorphous, Ceftibuten Hydrate. The name of this manufacturer has changed from NECTAR LIFESCIENCES LIMITED (SPOR ORG ID: 100019097; SPOR LOC ID: 100029430) to CEPH LIFESCIENCES PRIVATE LIMITED (SPOR ORG ID: 100056505; SPOR LOC ID: 100101295)

***2025-05-05***

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

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***Confidential***
***Spanish Agency Of Medicines And Medical Devices***
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