Health And Youth Care Inspectorate

Report No: ***EDQM/H 24/2023-039-P01***

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 Netherlands confirms the following:
The manufacturer: ***Anhui Bayi Chemical Industry Co. Ltd.***
Site address: ***Mokehou Industrial Park, No 1369 Jintuo Road, Huaishang, Bengbu, 233000, China***
OMS Organisation Id. / OMS Location Id.: ***ORG-100033909*** / ***LOC-100078504***

Other
The inspection was performed in the frame of the EDQM inspection programme

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2024-05-29***, 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 (EU) 2017/1572 and/or Commission Delegated Regulation (EU) 2017/1569, as reflected by the product categories stated in Part 2.Article 47 of Directive 2001/83/EC
- The principles of GMP for active substances referred to in Article 47 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.

EudraGMDP

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.

---

[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.*

EudraGMP

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**
	1.4.3 Other: active substance intermediate(en)

Manufacture of active substance. Names of substances subject to non-compliant:
4-AMINOPHENOL(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance:4-AMINOPHENOL	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: purification, 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

Part 3

1.Nature of non-compliance:

During the inspection 1 critical and 7 major deficiencies were found: Critical: 1 The inspection revealed a substantial number of severe GMP violations in various areas. This indicated not only a substantial lack of GMP knowledge by the firm, but also a shortfall of QA oversight. Together with the repeated statement of the firm's management that the firm manufactures chemicals and is not involved in GMP activities, which violates the firm's own commitment to follow EU GMP as outlined in the above-mentioned CEP application, a significant impact on the quality of the N-1 intermediate p-aminophenol and a negative impact on the final API paracetamol cannot be excluded. Major: 2 Contamination of the firm's final product, i.e. the intermediate p-aminophenol (PAP), was certain based on the condition of filter cloths and the dilapidated state of the areas surrounding the four air inlets. Two of them are located in a small room on the roof which supplies the air that is to be heated up and used to dry the wet PAP cake in a continuous drying process. The other two are located outside, protected only by a roof, and supply the air for the transport of dried PAP. Before transporting the dried intermediates, the air passes through an air handling unit (AHU). The contamination was evidenced as follows: a. One filter cloth of each set of air inlets showed substantial damage/large gaps. As a consequence, air from the outside environment came into direct contact with the product to be dried. The firm later explained that the cloths were intentionally destroyed to ensure enough air supply in case the filters became clogged. b. All four ceilings above the inlets released paint flakes. The two inlets located in the rooms were in a horizontal position; therefore, large paint flakes could be found on the intact parts of the filter cloths. c. Bins full of dust and dirt, brooms, etc. were found in close proximity to one air inlet, protected only by a room. Considering the enormous amount of air needed for the drying operation, this particulate matter could be sucked onto the filter cloths causing clogging or, in the case of damage, further distribution towards the AHU. Another risk factor contributing to a potential negative impact on the air being filtered is the limited protection of the air inlet itself by a roof made only of corrugated steel. Therefore, particles from the wind, dust and dirt accumulated on the roof could contribute to the clogging of the filter. d. According to the design drawing shown, a 3rd filter should be installed in the AHUs. This was not the case for the AHU that was opened. The other major 6 deficiencies include: - insufficient maintenance resulting in serious contamination and corrosion of the plant and equipment; - improper change management lacking sufficient level of detail, retrospective risk assessments missing major risks, and lack of evaluation of effect of major changes on the quality of the product; - major flaws in the company's approach to process validation resulting in the process being considered non validated; - alarms generated by the automatic process control room can lack proper assessment, and an overview of alarms are not available to QA during batch release.

Action taken/proposed by the NCA

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

The manufacturer was removed as manufacturer of active substance intermediate from CEP 2000-124 for Paracetamol.

Others

The clients using the intermediate 4-aminophenol (para-aminophenol), the intermediate of Paracetamol, from ANHUI BAYI CHEMICAL INDUSTRY CO., LTD. to synthesize paracetamol, and the MAHs of the finished products using this paracetamol, should assess the potential impact on their finished product considering product quality and risk to the patient. This should in particular include an assessment of the risk of any foreign matter in Paracetamol based on the potentially contaminated intermediate 4-aminophenol.

Additional comments

The inspection was performed in the frame of the EDQM inspection programme

Products manufactured at site, if known	Products	Dosage Form	Reference Member State, National or EMA
Human Medicinal Products	paracetamol		

2024-08-16 Name and signature of the authorised person of the

Competent Authority of Netherlands

Confidential
Health And Youth Care Inspectorate
Tel:***Confidential***
Fax:***Confidential***

EudraGMP