National Agency For The Safety Of Medicine And Health Products

Report No: ***FR_001_NCR_2024***

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 France confirms the following:
The manufacturer: ***Haimen Pharma Inc.***
Site address: ***No 163 Zhuhai Road Binjiang Street, Haimen District, Nantong, 226100***
OMS Organisation Id. / OMS Location Id.: ***ORG-100041867*** / ***LOC-100069036***

Other
(Human) DIRECTIVE 2001/83/EC - Article 111 (4)

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2023-08-25***, it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

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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;	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.13 Tablets
1.5	**Packaging**
	1.5.1 Primary Packaging 1.5.1.13 Tablets
	1.5.2 Secondary packaging
1.6	**Quality control testing**
	1.6.2 Microbiological: non-sterility *1.6.3 Chemical/Physical*

Clarifying remarks (for public users)

The inspection scope was limited to the facilities where POSACONAZOLE tablets are manufactured and where "POSACONAZOLE ELC 100 mg, comprimé gastro-résistant" would have been manufactured including mainly receipt, storage, manufacturing workshop n°1, quality control and quality systems. Signatory: Mr Guillaume Renaud, director - Inspection division. The ANSM does not issue hard copy of this statement.

Part 3

1.Nature of non-compliance:

Four critical deficiencies were raised : 1) poor handling of deviations (3 recorded in 2022, 0 in 2023). However, inspectors noticed 7 incidents which should lead to deviations, such as rust on clean Posaconazole punches, inner of coating pan still wet 7 days after cleaning ; 2) high contamination risk in the cleanroom of the microbiological laboratory : 3 plastic boxes found filled with water and detergent (~40L). Boxes are used to clean the media reusable bottles. One box was full of glass bottles, water was turbid and there is no maximum duration for it to remain in the box. 3) high contamination risk in the microbial laboratory facilities : black filamentous traces observed on the wall above the autoclave. Also black and white traces found on empty reusable settle plates, packaged as ready to be sterilized. 4) poor management of API manufacturer : last audit of Posaconazole API manufacturer performed in April 2020 was not against EU GMP and findings included 2 criticals and 7 majors. Even if falsified sampling testing results were found during the audit, no follow up was done. Fourteen major deficiencies were also raised : 1) identification test performed only on composite sample for excipients ; 2) planned deviation allowed use of new Posaconazole API source on production lines even if the major change control, opened 7 days before, asked for several actions to be completed before ; 3) european GMP training not performed for employees ; 4) balances from the dispensing area moved without any restriction ; 5) deficient Posaconazole punches storage, maintenance and cleaning (rust, no protection against damage, cleaning method not validated) ; 6) coating pan in a bad state : still wet whereas cleaning done 7 days before, rust on the axis ; 7) data integrity issue with HPLC Empower software set up ; 8) microbiological laboratory incubators observed with settle plates inside closed plastic boxes ; 9) remaining raw material storage condition is not guaranteed after sampling, because commercial bags resealed with a machine found not qualified with black spots. 10) Neither checks performed for identity and conformity on packaging materials on delivery to the manual secondary packaging department before use, nor checks as IPC. 11) Microbiology not considered for equipments cleaning validation. Also the strategy applied for cleaning validation is based on an EHS approach, to define appropriated protection for workers according to hazard level of molecules. 12) The MAH did not carry out any audit on HAIMEN site before the EU regulatory dossier of Posaconazole tablet 100mg was submitted. 13) Poor handling of purified water production unit for workshop OSD 1 : water temperature in the loop above 33°C since several weeks, no internal specifications and no alarm set for temperature and water velocity, sanitization made every week without requirements in case of major incident, conductivity and TOC never tested in QC except during initial qualification, no trend analysis for using points results ; 14) Deficient traceability in the master batch record of Posaconazole 100mg, lot 106Z012326, manufactured on June 20th 2023 as equipments cleaning labels are not included, detergent used not registered, and names of the 10 workers needed to perform manual secondary packaging not recorded.

Action taken/proposed by the NCA

Others

Refusal of the national marketing authorization request of “POSACONAZOLE ELC 100 mg, comprimé gastro-résistant”. According to the information provided by the site, no EU customer was identified for any medicinal product manufactured at the site. Third countries national competent authorities should evaluate the criticality of products being supplied by this manufacturing site and enact measures to ensure continued supply where appropriate. *** UPDATE: ANSM received a comprehensive action plan that addresses the issues raised during the inspection. This action plan was reviewed and was found globally acceptable. However, due to the absence of any national product on the French market and the absence of any pending application involving this site, ANSM will not perform a follow-up inspection of this site to ensure the effective implementation of this action plan.

Additional comments

Aim of this inspection was to assess compliance with EU GMP for the manufacturing of “POSACONAZOLE ELC 100 mg, comprimé gastro-résistant”. All activities associated with the manufacturing and quality control operations of the product were inspected in compliance with the EU-GMP Principles and Guidelines and European Pharmacopeia and market authorization application dossier (MAA dossier). The inspection scope was limited to the facilities where POSACONAZOLE tablets are manufactured and where “POSACONAZOLE ELC 100 mg, comprimé gastro-résistant” would have been manufactured including mainly receipt, storage, manufacturing workshop n°1, quality control and quality systems.

2024-02-12

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

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