Italian Medicines Agency

Report No: ***IT/NCR/API/01/2024***

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 Italy confirms the following:
The manufacturer: ***Terhormon S.p.A.***
Site address: ***Via Nibbiola Snc, Terdobbiate, 28070, Italy, GPS: 45.373733, 8.688543***
OMS Organisation Id. / OMS Location Id.: ***ORG-100015039*** / ***LOC-100023721***

Other
unannounced inspection

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2024-06-20***, 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.
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: active substances(en)

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

Part 3

1.Nature of non-compliance:
The company was not deemed compliant with EU GMP standards. The Pharmaceutical Quality System was found inappropriate in order to ensure the correct and effective application of GMP during the manufacture of the active substances and the complete and detailed traceability of materials and activities. A high number of lacks were found in cleaning and maintenance operations in the production and storage areas and there were several gaps in traceability at different steps of product lifecycle. In addition to that, managerial responsibilities were not clearly defined. After the inspection carried out in February 2024, the Company did not put in place an adequate PQS to remove deviations and many of them were also raised during the inspection carried out in June 2024. Inspection Outcome: Besides 9 deviations raised in the previous inspection (7-9 February 2024) and not corrected, 14 major deficiencies (and 2 other deviations) were identified during the inspection carried out in 18-20 June 2024. These related to the following areas: 1) Pharmaceutical Quality system not adequate 2) Non holistic approach in CAPA plan submitted from the previous inspection (February \2024) 3) Lack of traceability of 900 kg (equivalent to 18 drums) of pancreatin AS 4) Replacement of environmental monitoring sheet 5) Uncleaned crude area for AS production 6) Ineffective pest control 7) Poor maintenance of equipment and facilities 8) Lack of traceability in maintenance plans 9) Uncontrolled documents (i.e. logbook) and unblocked excel sheets 10) Approval of production steps before the equipment cleaning results 11) Cleaning between different campaign not performed 12) Unidentified BR for no pharma use 13) Lack of reconciliation of materials after transfers 14) Warehouse logbooks inadequate to trace the materials

Action taken/proposed by the NCA

Suspensionof the manufacturing authorisation No. aM103/2023in Full
AIFA suspended the authorisation N° aAPI- 90/2023 issued date 2023/07/31 related to the manufacturing of biological active substance: Pancreatin Withdrawal of current valid GMP certificate No: IT-API/191/H/2023 issued date 2023/07/31.

Recall of batches already released
The competent Authority of Italy deems not to recall the batches of AS already distributed. Each involved NCA should evaluate following assessment conducted in conjunction with MAHs if a recall of medicinal product is needed.

Prohibition of supply
Shortage of the medicinal products containing the active substance manufactured by Terhormon is considered a real risk. Lack of alternative service providers and risk of shortage should be assessed case by case. Each involved NCA should evaluate following assessment conducted in conjunction with MAHs to recommend a full retest of the active substance manufactured by Terhormon before using for the further processing. In case of failure, the Supervisory Authority has to be informed.

Additional comments
This manufacturer for active substance should not be approved in any new/ongoing applications until appropriate corrective action will be implemented and GMP compliance will be resumed.

2024-07-03

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

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