Spanish Agency For Medicines And Health Products

Report No: ***NCF-II/NC2024/01/CAT***

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. 94(2) of Regulation (EU) 2019/6 as amended
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of Spain confirms the following:
The manufacturer: ***Menadiona S.L.***
Site address: ***Poligon Industrial Mas Puigvert S/N, Palafolls, 08389, Spain***
OMS Organisation Id. / OMS Location Id.: ***ORG-100015162*** / ***LOC-100023846***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2024-07-10***, 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 51 of Directive 2001/82/EC and 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
Veterinary 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:

AZAPERONE(en)
CLOBENZOREX HYDROCHLORIDE(en)
CLOMIFENE CITRATE(en)
CHLORTALIDONE(en)
L-LYSINE AESCINATE(en)
GABAPENTIN(en)
IPIDACRINE HYDROCHLORIDE HYDRATE(en)
LAMOTRIGINE(en)
MEBHYDROLIN NAPADISILATE(en)
MENATETRENONE(en)
NITROFURAZONE(en)
QUETIAPINE FUMARATE(en)
TIAZOTIC ACID MORPHOLINUM SALT(en)
CALCIUM SACCHARATE TETRAHYDRATE(en)
ALL-RAC-PHYTOMENADIONE(en)
MENADIONE SODIUM BISULFITE(en)
FURAZIDIN(en)
FURAZIDIN SODIUM(en)
CLOSANTEL SODIUM DIHYDRATE(en)
RONIDAZOLE(en)

Part 3

1.Nature of non-compliance:

A follow up GMP inspection of the site was performed on July 2024 (01, 02, 03, 04, 05, 08, 09 and 10). This inspection was focused on EU-GMP compliance verification related to the active substances manufacturing activity. During the inspection not compliance with EU-GMP-Part II requirements was detected. A total of twenty four (24) deficiencies were identified, four (4) of which were classified as critical deficiencies and ten (10) as major deficiencies. Critical deficiencies were observed in the manufacture of the active pharmaceutical ingredients furazidine sodium and ronidazole, where the last steps of the manufacturing process were carried out in a facility which did not comply with GMP Part II requirements. Critical deficiencies were also observed in the management of batch reprocessing, where was found out data and documentation related to reprocessing activities hidden and falsified. A summary of the critical deficiencies follows: a) The final step of manufacturing of the pharmaceutical active ingredient ronidazole, is carried out in a facility that does not comply with the GMP Part II (the area is not classified and the equipment cleaning procedures have not been validated or verified prior to use), and none of the batches manufactured and certified complied with the ICH regarding residual solvents. b) The final step of manufacturing of the pharmaceutical active ingredient furazidin sodium is carried out in a facility that does not comply with the GMP Part II (the area is not classified and the cleaning equipment procedures have not been validated or verified prior to use). c) Systematically, the company's management obstructed and blocked the actions of the inspectors not providing complete and clear information in response to the inspectors' questions. Evidence of falsified and hidden documents and destroyed electronic documentation and files were found in relation with the reprocessing of batches of active pharmaceutical ingredients. Deficiencies, classified as mayor, were also identified in quality management, cleaning validation and the cleaning validation of campaigns, the state of cleaning and maintenance of the facilities, the management and control of cross-contamination, the integrity of data, the management of reprocessing activities and the management of out-of-specifications.

Action taken/proposed by the NCA

Recall of batches already released

The recall of all batches of ronidazole and furazidine sodium, and the batches 3114/30010, 3114/30011 and 3114/30012 of ipidacrine hydrochloride hidrate and the batch number 3117/30018 of clomiphene citrate is recommended.

Prohibition of supply

In the case that the competent authority of a country considers it necessary and upon express request they may make use of the available stock of these products.

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

MENADIONA at Palafolls has 4 valid CEP issued by EDQM. The CEP affected are: - QUETIAPINE FUMARATE R1-CEP 2015-334 - Rev 00 - CHLORTALIDNE CEP 2017-285 Rev 01. - CLOMIFENE CITRATE R1-CEP 2003-193 - Rev 04 - AZAPERONE CEP 2017-190 Rev 01 EDQM is contacted in order to consider whether any actions on the CEPs are necessary. EDQM will be informed of the future inspection outcome and to allow performing the assessment required to decide whether restoring of the CEPs should take place or not.

Others

All importing and manufacturing activities of active pharmaceutical ingredients and / or intermediates that are carried out at the MENADIONA S.L. manufacturing site at Palafolls have been suspended as a precautionary measure. Likewise, the activity of distribution and sale of any active pharmaceutical ingredient or intermediate that has been manufactured, in whole or in part, in the facilities of MENADIONA S.L. has been suspended as a precautionary measure. These measures will be maintained until all the deficiencies observed in the inspection have been corrected and it is verified through a new inspection, that the company has an effective quality assurance system duly implemented and compliant with the EU-GMP part II. Recommendations/proposed actions: Manufacturers of finished medicinal products are recommended to carry out a full testing on every container of active substance or intermediate received from the manufacturing site of MENADIONA SL, ensuring that a representative sampling is used (including sampling at different depths in the drum) In case of out of specification results are detected, NCA should be informed by the MAH. In case of out of specification results are detected, national competent authority (NCA) should be informed by the marketing authorization holder (MAH). It may also be considered that all batches of the finished

medicinal products in which these active substance or intermediates be used have to beare included in the “on going” stability studies. NCA should be informed by the MAH if out specification results or tendencies are observed during these studies. If an Out of Specification test result (OOS) is reported by the MAH, the procedure would be the same that is applicable to other notifications of OOS results. In case coordinated regulatory action is deemed necessary by a Member State, the Compilation of Community Procedures on Inspections and Exchange of Information (CoCP) (i.e. non-compliance, recall) should be followed.

Additional comments

Current EU-GMP part II certificate NCF-II/2410/001/CAT has been withdrawn. This statement of non-compliance is signed by Generalitat de Catalunya, and sent to Eudra GMDP by AEMPS

2024-09-11

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

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Confidential
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