Malta Medicines Authority

Report No: ***MT/002/NCR/2023***

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 Malta confirms the following:
The manufacturer: ***Beximco Pharmaceuticals Limited***
Site address: ***Tongi, 126 Kathaldia Auchpara, Gazipur, 1711, Bangladesh***
OMS Organisation Id. / OMS Location Id.: ***ORG-100014998*** / ***LOC-100060917***

Other
(Human) Application for a GMP certificate for MA registration in Malta (Latanoprost 0.005mg/ml + Timolol 5mg/ml eyedrops)

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2023-08-01***, 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;

1.1	Sterile products
	1.1.1 Aseptically prepared (processing operations for the following dosage forms)
	1.1.1.6 Other: Eye drops(en)

Part 3

1.Nature of non-compliance:

PharmSol Europe Limited, Malta as proposed MAH is reserved a dossier filing slot in Malta (Malta as RMS) for the product Latanoprost 0.005 mg/ml + Timolol 5 mg/ml eyedrops in the month of October 2023 stating Beximco as finished product manufacturer (assigned DCP no. is MT/H/0708/001/DC). PharmSol Europe as Applicant applied for a GMP certificate with the scope of aseptically prepared sterile medicinal products, small volume liquids, eye drops with Malta Medicines Authority. A product specific GMP inspection with the scope of Latanoprost 0.005 mg/ml + Timolol 5mg/ml eyedrops (Latanoprost & Timolol PharmSol 0.05mg/ml+5mg/ml Eye Drops) was conducted on 28th July – 1st August 2023. The inspectors found one critical, three major and fifteen other deficiencies. The outcome of this inspection was discussed at the Inspection Review Group (IRG) at the Malta Medicines Authority who decided that a Statement of Non-Compliance with the principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC is to be issued about the site. Main inspection findings: One critical and three major deficiencies were found during the course of this inspection. The critical finding is related to: -the TAC Vista Building Management System (BMS), version 5.1.7.219 was not working and there is some issues with facility design -Environmental (EM) conditions such as temperature, relative humidity and differential pressure cannot be continuously monitored since BMS system is not working. All specific alarm files (.txt) and audit trails (named as `Events`) have been lost. -Currently actual temperature, humidity and delta pressure values in the facility are documented manually only twice daily. If alert levels are exceeded, alarms are not triggered, although there are issues with power supply as well (from 2019 twenty-one deviations were opened related to power cuts and failures). When power cut occurs, it takes 5-10 minutes to recover the electricity. This issue was also highlighted during the last EU GMP inspection. The three major deficiencies were found in the areas of: -GMP manufacturing activities, including aseptic processes in the Vision Unit (BLD-002) and their validation -Quality Management System (QMS) -Data integrity For further details the post-inspection letter (dated: 11th August 2023) that lists all findings is available by request to National Competent Authorities. Assessment of first CAPAs for critical finding: The company`s first CAPA-plan related to the critical finding was received on 17th August 2023. After evaluation the Inspection Team found them unsatisfactory since no proposal for final preventive actions were proposed to avoid re-occurrence of the same issues (re critical deficiency). Second CAPAs with supporting evidence documents related to the critical finding will be submitted by Beximco on 31st October except for installation of new BMS for which target timeline, 31st March 2024 was provided. Assessment of main inspection findings on concerned medicinal products: The critical, major and other deficiencies, indicate that the sterility assurance of products manufactured in the inspected block cannot be guaranteed at all times in view that: the environmental monitoring, including delta-p, is not continously monitored, with frequent electicity failures being experienced during which differential partial presssures fail, aseptic process stimulations (APS) carried out until June 2023 do not reflect the actual practice during asceptic manufacturing, deviations are not always logged and preventive actions are either missing or when taken are generally weak, plus issues with the integrity of retained GMP related data were also identified, amongts other deficiencies as listed in the post inspection letter. These all indicate strongly towards a lack of proper quality assurance as required with respect to the manufacture of sterile products.

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. DE_BW_01_GMP_2020_0001
It is recommended to withdraw issued GMP compliance certificate DE_BW_01_GMP_2020_0001 (issued by Baden – Württemberg (Regierungspräsidium Tübingen Leitstelle Arzneimittelüberwachung) on 27th January 2020.

Prohibition of supply
Prohibition of supply to EU/EEA markets.

Others
No new marketing authorisation applications, line extensions or variations to existing marketing authorisations applications should be authorised with this site as a site of manufacture until the non-compliance is in place.

2023-09-07

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

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Confidential
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