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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

- The principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572 and Commission Delegated Regulation (EU) 2017/1569

(1) The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.

Part 2

Human Medicinal Products

1 NON-COMPLIANT MANUFACTURING OPERATIONS

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

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.

Teleconference Date:	Teleconference Time (CET):	Dial in no.:

2023-09-07

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

Confidential

Malta Medicines Authority

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