Regierung von Oberbayern

Report No: ***DE/NCR/BY_04//1/2020***

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 Germany confirms the following:
The manufacturer: ***Symbiotec Pharmalab Ltd.***
Site address: ***385/2 Pigdamber, Near Hotel Mashal, Off A.B. Road, Rau, Indore (M.P.), 453331, India***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2019-10-22*** , 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 47 of Directive 2001/83/EC .

[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

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) 1.1.1.2 Lyophilisates
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility *1.6.3 Chemical/Physical*

4. Non-Compliant Other Activities - Active Substances :

The non-compliance Statement applies to the following active pharmaceutical ingredients (API), which are manufactured at Rau site: Beclometason Dipropionat, Betamethason Dipropionat, Betamethason Valerat, Clobetason Butyrat, Clobetasol Propionat, Cloprednol, Deflazacort, Desoximetason, Halobetasol Propionat, Hydrocortison Hydrogensuccinat, Methylprednisolon Acetat, Methylprednisolon Hemisuccinat, Mometason Furoat, Prednisolon Hemisuccinat, Prednisolon Sodium Phosphate, Triamcinolon Acetonid. It alsp applies to the sterile bulk medicinal products Hydrocortisone sodium succinate buffered 5 % sterile AND Methylprednisolone sodium succinate buffered 3% sterile.

Part 3

1. Nature of non-compliance:

The Non-Compliance Statement is being issued now, after company handed in CAPA plan, which contained acceptable CAPAs to some findings, but inacceptable findings to two critical findings and a finding concerning Handling of OOS. - Two critical and six major deficiencies were found concerning the following areas: Data integrity (1 critical), Deviation Handling (1 critical), Change Control Handling (1 major), Rooms and Equipment in sterile manufacturing area (1 combined major deficiency), Microbiological Monitoring in sterile manufacturing area (1 major), OOS Handling (1 major), Annual Product Review Handling (1 major), Aseptic Process Simulation (Media Fill) Handling (1 major) - 1st critical finding regarding Data Integrity was due to company's missing documentation of root cause analysis including risk analysis of recurrent OOS regarding sterility of sterile bulk products, which were found at customer in EU. Documentation presented during inspection was not complete and by far not sufficient. After inspection, company handed in a CAPA plan on 03.01.2020 including a risk analysis document, which was dated 08.01.2019. Hence, this document was either not handed over to the inspectors during inspection in October 2019 (although a risk analysis was requested several times) or the document was backdated. Either possibility is not acceptable. - 2nd critical finding was company failing to establish an adequate deviation documentation system. Since last inspection by Government of Upper Bavaria, only 12 deviations have been documented. 7 of these have been documented after findings in inspections by Government of Upper Bavaria and US FDA. This means that during only a few days of inspections, 58% of all deviations were documented, and on the remaining days of the year, only 5 deviations were documented. Company failed to report some deviations as such. Instead, documentation was as e.g. "equipment breakdown order". These events are neither documented nor tracked in any traceable way. For "equipment breakdown orders", no tracking list was available, the documentation of these events was discarded after resolution, no documentation of these events in the batch manufacturing record. Company also refused to report deviations as such, if they were already reported in other quality systems, e.g. within complaints. This is not acceptable, as all deviations need to be documented and tracked as such, also if they arise from another type of event. The potential underreporting of deviations had already been a finding in the inspection in November 2015. - 1st major finding was that the Change Control procedure was insufficient in that its completeness and its traceability could not be assured. - 2nd major finding was numerous defects and deficiencies regarding the rooms of the sterile manufacturing area. Each for itself would not constitute a major finding, but the sum of the deficiencies lead to classification as major. - 3rd major finding was the missing documentation of settle plate exposure time in the sterile manufacturing area. - 4th major finding was concerning the SOP about Handling of Out of Specification results. The SOP lacked some definitions and the procedures were not described in a clear and complete way. The SOP did not ensure that the handling of OOS was performed according to EU GMP Guideline. - 5th major finding was that different Annual Product Quality Reviews were compiled for the different markets and specifications. Overall Annual Product Quality Reviews for products, which have the same production process, were not compiled. - 6th major finding concerned the Aseptic Process Simulation (Media Fill). The SOP lacked clarity in some points, and the procedure defined in the SOP was not adhered to for the sterility OOS topic.

Action taken/proposed by the NCA

Prohibition of supply

is recommended, unless there are no alternative suppliers and there is a risk of shortage. Evaluation of risk of shortage lies within the responsibility of each national competent authority Full analysis according to final product specifications by medicinal products manufacturers is recommended for already purchased APIs and medicinal products.

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

to be decided by EDQM

Additional comments

Certificate No. DE_BY_04_GMP_2019_0017 to be withdrawn. Remark: Certificate's validity was limited until 31.10.2019 anyway. A GMP certificate will only be issued again after a successful re-inspection.

2020-03-24

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

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Confidential
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