Thüringer Landesamt für Verbraucherschutz (TLV)
Tennstedter Str. 8/9
99947 Bad Langensalza

Report No: DE/NCR/API/2018/TH-01

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of Information between National Competent Authoriies (NCAs) oft he EEA following the Discovery of serious GMP non-compliance at a manufacturerer[1]

Part 1

Issued following an inspection in accordance with
Art. 80(7) of Directive 2001/82/EC

The competent authority of GERMANY / THURINGIA confirms the following:
The manufacturer : **BFC BioPept-Feinchemie GmbH**

Site address: **Zum Birntal 1, 99998 Weinbergen, Germany**

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 2017-08-17 it is considered that it does not comply with the Good Manufacturing Practice requirements laid down in

- The principles of GMP for active substances referred to in Article 51 of Directive 2001/82/EC.

Part 2

3. NON-COMPLIANT MANUFACTURING OPERATIONS – ACTIVE SUBSTANCES

Manufature of Active Substances by Chemical Synthesis
3.1.1 Manufacture of active substance intermediates
3.1.2 Manufature of crude active substance
3.1.3 Salt formation /Purification steps

3.5 General Finishing Steps
3.5.1 Physical processing steps
Centrifuge / drying
3.5.2 Primary Packaging
3.5.3 Secondary Packaging

3.6 Quality Control Testing
3.6.1 Physical / Chemical testing

Active Substance: Carbetocine, Gonadoreline[D-Phe6]acetate, Peforeline, Denaverin-hydrochloride

Part 3
Nature of non-compliance:

During inspection from 16-Aug-2017 to 17-Aug-2017 five critical and twenty four major deficiencies were found.

Critical Deficiencies:

1. Serious gaps in the QA-system: Five major deficiencies (no. 1 to 5) were merged to "critical". It was to be estimated, that activities carried out on the site are not completely described and not completely implemented.
2. Personnel: There is no independence of QA.
3. Personnel: Responsibilities of key-personnel are not completely regulated
4. Equipment: There is no validation of computerized system "HPLC3".
5. Serious gaps concerning planning, execution and documentation of qualification and validation activities: several major deficiencies (no. 8 to 18) were merged to "critical".

Major Deficiencies (short summary due to the huge number of deficiencies):

1. Deviation Management is not completely regulated and not completely implemented.
2. CAPA-System is not completely regulated and not completely implemented: - Corrective measures accepted.
3. .Internal provisions related to change control are not complete or not appropriate.
4. Internal provisions relating Product Quality Review are incomplete. Actual PQRs have deficiencies in respect of content.
5. There is no action plan for the prevention of cross contamination not dedicated areas.
6. Personnel: Internal provisions relating qualification and training are incomplete.
7. Documentation: Gaps concerning the control of QA-related documents.
8. There are no provisions for clearance and disinfection of a laminar air flow bench.
9. Premises: There is no microbial monitoring of the laminar air flow working bench and "clean room".
10. Requalification of air ventilation-system was not conducted after a critical incident.
11. There are no written instruction Packing of preparative HPLC columns is not
12. Equipment: Qualification of a new synthesis reactor was conducted in 2017 in a accompanying way. Activities are not completely documented.
13. There is no revalidation of the manufacturing process (Denaverine) after scale up.
14. Cleaning validations / cleaning verifications are not regulated in a proper way.
15. Documentation according to the state of the art in science and technology is not available for qualification of HPLC-systems in QC.
16. No qualification documentation for another HPLC-system used for preparative isolation.
17. There are no written instructions for the sterilization of glass vials used for sampling.
18. Water treatment: Deficiencies concerning production and storage of water.
19. Hygiene: There are lacks concerning the provisions for the use of cleaning equipment and cleaning materials.
20. There are no detailed instructions for packaging processes.
21. Lacks in the documentation in labor journals.
22. Maintenance and calibration: Several Lacks.
23. QK: Serious lacks concerning the ongoing stability program.
24. Gaps in the self inspection system.

Action taken/proposed by the NCA:

Refusal to issue a new GMP certificate.

3. Additional comments

It is known that the manufacturer is an API-supplier of the drug manufacturer / Marketing Authorization Holder Veyx-Pharma GmbH, Söhreweg 6, 34639 Schwarzenborn (Germany).
Although the huge number of deficiencies, there is no evidence that the quality of manufactured APIs is affected. This non-compliance statement is not associated with a proposal for a prohibition of supply.

2018/02/09

Name and signature of authorized person of the Competent Authority of Thuringia

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