Agencija za Lijekove i Medicinske Proizvode

Report No: ***UP/I-530-10/16-03/11; 381-10-05/151-16-03***

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 Croatia confirms the following:
The manufacturer: ***POLYDRUG LABORATORIES PVT. LTD.***
Site address: ***Plot No. 37, Anand Nagar, M.I.D.C., Ambernath (East), Maharashtra, IN - 421 506, India***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-02-24*** , 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;

1.4	Other products or manufacturing activity
	1.4.1 Manufacture of 1.4.1.4 Other: active substance(en)

Manufacture of active substance. Names of substances subject to non-compliant :
CHLOROBUTANOL HEMIHYDRATE(en)

Clarifying remarks (for public users)

The active substance in scope of inspection was Chlorobutanol Hemihydrate. Manufacturing process of the other active substances and intermediates manufactured on the site were not in the scope of the inspection. The Company is engaged in manufacturing of the following APIs and Intermediate: Metoprolol Tartrate, Metoprolol Succinate, Losartan Potassium, Chlorobutanol Hemihydrate, Chlorobutanol Anhydrous, Fluconazole, Carisoprodol, Metoprolol Base – intermediate. Ferrous Fumarate – manufacturing activities are discontinued, available stock has been distributed.

Part 3

1. Nature of non-compliance:

This inspection was performed in the framework of EDQM's inspection scheme and the CEP dossier for Chlorobutanol hemihydrate / R0-CEP 2009-112-Rev 00 / The inspection was requested by the Company aimed to demonstrate compliance to EU GMP after the initial inspection performed in 2015 which led to the issuance of a Statement of GMP Non-Compliance by the Slovenian authority (Report No: INSP 2015-002 P01). The inspection from February 2016 identified in total 22 deficiencies against EU GMP Part II and relevant annexes, of which 4 major related to: Quality Management, Documentation, Materials Management/Storage, Validation. Also, the Company did not follow CAPA from previous inspection in the way as submitted to EDQM to address the observations from the inspection from 2015. The initial CAPA submitted for the current inspection from 2016 was found insufficient for the following deficiencies: -Major: QM/Release of repacked batches, Validation of Computerised Systems -Other: Repackaging of batches, Reduced testing of APIs, HPLC analysis (manual integration), Cleaning validation After receipt of the additional information provided by the Company to the inspection team, the issues regarding the release of batches, reduced testing of APIs and manual integration/data integrity were still considered as not adequately treated and thus still as not in compliance to EU GMP. Overall it can be concluded that an appropriate level of compliance to GMP is not implemented.

Action taken/proposed by the NCA

Requested Variation of the marketing authorisation(s)
Removal from marketing authorizations should be considered. This is repeated Statement of non-compliance with GMP and in 2015 proposed action was "change of API supplier" so check previous conclusion about the impact to the market.

Prohibition of supply
No further batches to be supplied to the market whilst this statement remains in force.

Suspension or voiding of CEP (action to be taken by EDQM)
Withdrawal of CEPs as the result of the repeated GMP non-compliance : Chlorobutanol hemihydrate / R0-CEP 2009-112-Rev 00; Metoprolol tartrate /R0-CEP 2009-152-Rev 01; Metoprolol succinate / R0-CEP 2009-170-Rev 01; Ferrous fumarate / R0-CEP 2010-147-Rev 00; Fluconazole / R0-CEP 2010-247-Rev 00.

2016-11-11

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

---

Confidential
Agency for Medicinal Products and Medical Devices of Croatia
Tel: ***Confidential***
Fax: ***Confidential***