Medical Products Agency

Report No: ***4.1.2-2014-051974***

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 Sweden confirms the following:
The manufacturer: ***AstraZeneca Pharma India Ltd.***
Site address: ***´Sanjeevni´ 12th Mile on Bellary Road,, Bangalore, 560063, India***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-01-19*** , 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 Substances(en)

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

Part 3

1. Nature of non-compliance:

The API manufacturing process was not acceptably validated and was not under control after the validation. The concerned batches have been sent to the EEA (Sweden) and to a third country (China). During the inspection, 24 deficiencies were found. None of the deficiencies was critical but 4 were major. The 4 major deficiencies were found in the areas of documentation routines and data integrity (2), design and maintenance (1), validation (1). After three CAPA responses from the company the major deficiency regarding validation still remains.

Action taken/proposed by the NCA

Recall of batches already released
Risk assessment: The only API manufactured at the site is Terbutaline sulphate. The API is used for the manufacture of non-sterile and sterile finished products. In total five validation runs were executed between February and November 2014. The first four validation runs failed and included several OOS results, adjustments, test batches and inappropriate root cause analysis. After the fifth validation run the company stated that the process was successfully validated, despite a specification change (exclusion of a melting range) was necessary to approve the validation. After the validation the rejection rate was very high (approximately 40%) and for this reason the company stopped the production in December 2014. On 2015-10-30 the company confirmed that a definite root cause has still not been identified and that no further manufacturing of the API is planned for this site. Eight API batches were released from the site in India without any restriction but they were retested and released a second time in Sweden. After this retest, one of the three validation batches was rejected but the validation was still not questioned by the company. According to the company seven batches have been sent to China and used for manufacturing finished products at the AstraZeneca site in Wuxi, China. The finished product (Bricanyl Tablets) has been declared to be intended for the Chinese market only. The issuance of this NCS is not expected to have a negative impact on the supply to the EEA. Risk Mitigating Actions: -In June 2015 the company was recommended to recall all Terbutaline Sulphate batches not supported by an acceptable validation. The batches have not been recalled but the further use of them has been stopped. All API batches manufactured during the year 2014 are concerned. This includes all batch numbers starting with TAIO and TABO. The O stands for year 2014. -Information about the NCS will be sent to the CFDA. A first information letter about the GMP deficiency was sent from the MPA to the CFDA in July 2015. -The concerned authority in India will be requested to recall the concerned written GMP confirmation. -Publication of this NCS is expected to prevent the API and finished product from being imported to the EEA from China. -The distribution and destruction records for any remaining API-batches will be followed-up. -It is recommended that the site is not approved in any new or ongoing applications before a re-inspection has confirmed GMP-compliance.

Prohibition of supply
The concerned API-batches or finished product containing the API should not be imported to the EEA.

Others
The last valid EU GMP certificate, issued by MPA Sweden, expired in February 2015.

Teleconference Date		**Teleconference Time (CET)**	N/A	**Dial in no.**	N/A

2015-12-11

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

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