Italian Medicines Agency

Report No: ***IT/NCR/API/1/2017***

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 Italy confirms the following:
The manufacturer: ***KORES (INDIA) LIMITED***
Site address: ***Plot Nos. 58/1, 58/2, 59A, 65A, 65B, 65C & 66A, M.I.D.C. Industrial Area Dhatav, Roha, Maharashtra, 402 116, India***
DUNS Number: ***67-760-4350***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2017-03-04*** , 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;	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.17 Other: active substances(en)

Manufacture of active substance. Names of substances subject to non-compliant :
AMBROXOL HYDROCHLORIDE PH. EUR.(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : AMBROXOL HYDROCHLORIDE PH. EUR.	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps : filtration and crystallization
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : drying, milling and sieving 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.2 Microbiological testing excluding sterility testing

Part 3

1. Nature of non-compliance:
Major deficiencies were found in the following areas: electronic and paper analytical data integrity, QC activities, computerised systems security, analytical and process data manipulation, personnel, deviations and OOS management leading to a serious risk for public health.
Action taken/proposed by the NCA **Requested Variation of the marketing authorisation(s)** It is recommended to assess the opportunity of requesting variation to the marketing authorisation in order to delete or substitute this manufacturer of the active substance **Recall of batches already released** If there are alternative suppliers and there is no risk of shortage, recall of medicinal product should be evaluated by involved NCAs' following assessment conducted in conjunction with MAHs. Given the nature of non-compliances,

assessment should include a complete retest of all imported batches of active substance

Prohibition of supply
Due to the nature of the non compliance prohibition of supply is recommended, unless there are no alternative suppliers and there is a risk of shortage.

Suspension or voiding of CEP (action to be taken by EDQM)
All the CEPs suspension recommended by the inspection team was officially endorsed by the Ad Hoc Committee on 16 March 2017

Others
This supplier should not be approved in any new/ongoing application.

Additional comments
This inspection was performed in the framework of the CEP dossier for the manufacture of Ambroxol hydrochloride.The found deficiencies could affect the other APIs manufactured at the site listed below: Doxofylline, Etofylline, Acefylline, Glimepiride, 3-Methylxanthine, 2-Amino-3,5-dibromobenzaldehyde, 8-ChloroTheophylline,8-Benzyl Theophylline, Bromhexine HCl, Acebrophylline, Theophylline, Piperazine/Acepifylline, Theobromine, Orphenadrine Citrate/ Base, Pamabrom,Ivabradine HCl, Dorzolamide Hydrochloride.

2017-05-09

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

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