檔　　號：
保存年限：

正本

衛生福利部食品藥物管理署　函

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受文者：中華民國西藥代理商業同業公會

發文日期：中華民國106年5月25日
發文字號：FDA風字第1061103120A號
速別：
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份

主旨：有關印度原料藥廠「KORES (INDIA) LIMITED」（廠址：Plot Nos. 58/1, 58/2, 59A, 65A, 65B, 65C & 66A, M.I. D.C. Industrial Area Dhatav, Roha, Maharashtra, 402 116, India）經國際通報違反GMP乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、義大利衛生主管機關Italian Medicines Agency（IMA）於106年3月4日查核旨揭原料藥廠，判定違反GMP，並於106年5月10日發布旨揭藥廠「STATEMENT OF NON COMPLIANCE WITH GMP」警訊（詳附件）。

二、承上，義大利IMA已啟動相關後續處置，包括：

(一)建議使用旨揭原料藥廠原料藥之製劑產品，應評估變更原料來源。

(二)對於使用旨揭藥廠原料藥之製劑廠，倘若有其他可替代之原料來源或無缺藥疑慮，相關產品應評估回收；另，應對廠內庫存之原料藥執行全項檢驗。

(三)旨揭原料藥廠製造之相關原料藥應暫停出貨。

(四)凍結旨揭藥廠生產原料藥之CEP證明文件。

三、鑑於旨揭原料藥之製造品質恐無法符合GMP之要求，可能對藥品製造品質帶來影響與危害，請轉知所屬會員釐清相關輸台製劑產品是否使用旨揭原料藥廠所生產原料藥，並應依說明段二所述辦理。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、中華民國藥品行銷暨管理協會
副本：

署長吳秀梅

Italian Medicines Agency

Report No: *IT/NCR/API/I/2017 rev.1*

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;	
1.4	**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 :
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, Palnabromlvabradine HCl, Dorzolamide Hydrochloride.

2017-05-10

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

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Confidential
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