

正本

檔 號：  
保存年限：

衛生福利部食品藥物管理署 函

機關地址：11561 臺北市南港區昆陽街161-2號

傳 真：0227877178

聯絡人及電話：蘇子婷 0227877148

電子郵件信箱：daisyhaha@fda.gov.tw

10668

106台北市大安區敦化南路二段128號15樓

受文者：中華民國藥品行銷暨管理協會

中華民國藥品行銷暨管理協會
收文日期：105年8月31日
本文件保留： <input type="checkbox"/> 1M. <input type="checkbox"/> 3M. <input type="checkbox"/> 6M
<input type="checkbox"/> 1Y. <input type="checkbox"/> 3Y. <input type="checkbox"/> 5Y
<input type="checkbox"/> 未定 <input checked="" type="checkbox"/> 永久

發文日期：中華民國105年8月29日

發文字號：FDA風字第1051104723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「Artemis Biotech (A Division of Themis Medicare Limited)」(廠址：Industrial Development Area Plot No. 1&5 Jeedimetla, India-500 055 Hyderabad, Telangana) 經國際通報嚴重違反GMP乙案，詳如說明段，請轉知所屬會員知照。

說明：

- 一、歐洲理事會European Directorate for the Quality of Medicines & HealthCare (EDQM) 併同德國衛生主管機關Landesamt für soziale Dienste Schleswig-Holstein查核旨揭原料藥廠，判定嚴重違反GMP，並於105年8月11日正式發布「DECISION TO SUSPEND A CERTIFICATE OF SUITABILITY」，凍結(SUSPEND)下列品項之CERTIFICATE OF SUITABILITY (CEP) 品質證明文件。
  - (一)Simvastatin Antioxidant Butylated Hydroxy Toluene 0.01%。
  - (二)Simvastatin Butylated Hydroxy Anisole 50-150 ppm。
  - (三)Simvastatin Butylated Hydroxy Anisole 0.18-0.22%。
- 二、德國Landesamt für soziale Dienste Schleswig-Holstein亦於105年8月12日發布「STATEMENT OF NON

COMPLIANCE WITH GMP」，受影響之原料藥品項為「Simvastatin」（詳如附件）。

三、承上，且德國Landesamt für soziale Dienste Schleswig-Holstein已啟動相關後續處置，包括：

(一)使用相關原料藥之製劑產品許可證持有者應評估是否啟動回收，並評估是否有可替代之原料來源與缺藥疑慮；鑑於該廠違反GMP，已入庫之該廠原料藥，製劑廠應重新執行完整再驗程序。

(二)GMP狀態尚未改善完畢前，原料藥暫停出貨。

(三)使用旨揭原料藥廠原料藥之製劑產品，應考慮變更原料來源。

四、鑒於旨揭原料藥之製造品質無法符合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，並應依說明段三所述辦理。

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 姜郁美

**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<sup>1</sup>*

**Part 1**

Issued following an inspection in accordance with :  
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of Germany confirms the following:

The manufacturer: *Artemis Biotech (A Division of Themis Medicare Limited)*

Site address: *Industrial Development Area, Plot No. 1 & 5 Jeedimella, Hyderabad, 500 055, India*

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on *2016-06-29*, 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 .

<sup>1</sup> *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

<b>1 NON-COMPLIANT MANUFACTURING OPERATIONS</b>	
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;	
<b>1.4</b>	<b>Other products or manufacturing activity</b>
	<p>1.4.1 <i>Manufacture of</i></p> <p>1.4.1.4 Other: Active Substance (Simvastatin Antioxidant Butylated Hydroxy Toluene 0.01%)(en)</p>

Manufacture of active substance. Names of substances subject to non-compliant:  
***SIMVASTATIN(en) / ЧИМБАСТАТИН(bg) / SYMWASTATYNA(pl)***

<b>3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES</b>	
Active Substance : SIMVASTATIN	
<b>3.1</b>	<b>Manufacture of Active Substance by Chemical Synthesis</b>
	<p>3.1.2 Manufacture of crude active substance</p> <p>3.1.3 Salt formation / Purification steps: filtration, crystallisation, mixing with antioxidants</p>
<b>3.3</b>	<b>Manufacturing of Active Substance using Biological Processes</b>
	<p>3.3.4 Modification <i>Special Requirements:</i> 7. Other (starting material: Lovastatin, manufactured by fermentation)</p>
<b>3.5</b>	<b>General Finishing Steps</b>
	<p>3.5.1 Physical processing steps : drying, milling sieving (micronisation)</p> <p>3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)</p> <p>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)</p> <p>3.5.4 Other : Repackaging on customer demand</p>
<b>3.6</b>	<b>Quality Control Testing</b>
	<p>3.6.1 Physical / Chemical testing</p> <p>3.6.2 Microbiological testing excluding sterility testing</p>

## Part 3

**1. Nature of non-compliance:**

In total 35 observations were made by the inspection team over the course of the inspection. Five of them were categorised as major deficiencies and therefore potentially leading to a risk to the human and veterinary patient when using active pharmaceutical ingredients manufactured at the inspected site. - The installation and execution of an Enterprise Resource Planning System, hosting GMP relevant data but outside of the quality management system, demonstrated a lack of QA oversight. - Repackaging operations were conducted without any documentation and QA approval. - The issuance of labels for raw materials and APIs was found inadequately controlled. - Within the instrumental laboratory the Company violated basic principles on data integrity, i.e. manual integration without justification and QA oversight. - The Company's approach on the validation of computerised systems (Shimadzu LabSolutions) was considered as not in compliance with the requirements.

**Action taken/proposed by the NCA****Recall of batches already released**

No immediate recall is needed. Each involved NCA should evaluate, following assessment conducted in conjunction with MAHs, if a potential recall of medicinal product is needed. The risk based evaluation should take in account if there are alternative suppliers and potential risk of shortage. 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 non-compliances, prohibition of supply is recommended.

**Suspension or voiding of CEP (action to be taken by EDQM)**

This inspection was carried out as part of the EDQM inspection Programm. The impact of this NCS on the CEPs is to be decided by the EDQM. The concerned CEPs are Simvastatin Butylated Hydroxy Anisole 50 - 150 ppm R1-CEP 2006-091-Rev 00; Simvastatin Butylated hydroxy anisole 0.18-0.22% R1-CEP 2007-155-Rev 01; Simvastatin Antioxidant Butylated Hydroxy Toluene 0.01% R1-CEP 2003-257-Rev 03

**Others**

This supplier should not be approved in any new/ongoing applications. Each involved NCA should evaluate if the supplier should be removed from existing MAS.

**Additional comments**

This inspection was performed in the framework of the CEP dossier for the manufacture of Simvastatin Antioxidant Butylated Hydroxy Toluene 0.01% R1-CEP 2003-257. The company also produces Fumagillin (antibiotic manufactured from fermentation) for the French market. This API was not within the scope of this inspection.

2016-08-12

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

-----  
*Confidential*

*Landesamt für soziale Dienste Schleswig-Holstein*

*Tel: Confidential*

*Fax: Confidential*