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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(A21020000I105110214700-1.pdf)

主旨：有關PIC/S 警訊平台（PIC/S Rapid Alert System）通報印度原料藥廠「Anuh Pharma LTD」(廠址：E-17/3 & E 17/4 M.I.D.C., Tarapur, Thane District, Boisar, Maharashtra, 401 506, India) 嚴重違反GMP乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、法國衛生主管機關French Natinal Agency for Medicines and Health Products Safety（ANSM）於105年2月12日查核旨揭原料藥廠，判定嚴重違反GMP，並於105年3月24日發布「STATEMENT OF NON-COMPLIANCE WITH GMP」，受影響之原料藥品項包括「Ambroxol Hydrochloride」等共計16項（詳如附件）。

二、承上，法國ANSM已啟動相關後續處置，包括：

(一)建請義大利官方廢止原核發之GMP證明文件（No. IT/E/GMP/9/2013），再查，該GMP證明文件業已廢止。

(二)基於品質風險管理（Quality Risk Management）原則，相關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。

(三)基於品質風險管理原則，使用相關原料藥之製劑產品許可證持有者應評估啟動回收。

(四)製劑廠應暫停使用旨揭藥廠之原料藥。

三、另，歐洲EDQM亦於105年4月19日凍結（Suspend）旨揭工廠「Erythromycin Ethylsuccinate」、「Pyrazinamide」及「Erythromycin」相關品質證明CEP（the Certificate of Suitability）2年及暫停其他CEP申請案，待再次通過GMP複查後，始得恢復。

四、鑒於旨揭原料藥廠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，並應依說明段二所述辦理。

正本：中華民國藥品行銷暨管理協會、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

副本：2016-04-29 10:00:25

French National Agency for Medicines and Health Products Safety

Report No: *16MPP005NCS*

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
Art. 80(7) of Directive 2001/82/EC as amended

The competent authority of France confirms the following:
The manufacturer: ***Anuh Pharma LTD***
Site address: ***E-17/3 & E 17/4 M.I.D.C., Tarapur, Thane District, Boisar, Maharashtra, 401 506, India***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-02-12*** , 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 and Article 51 of Directive 2001/82/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 substance(en)

Manufacture of active substance. Names of substances subject to non-compliant :
ERYTHROMYCIN ETHYLSUCCINATE(en) / ÉRYTHROMYCINE (ETHYLSUCCINATE D')(fr)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES Active Substance : ERYTHROMYCIN ETHYLSUCCINATE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.2 Manufacture of crude active substance 3.1.4 Other : starting from erythromycin thiocyanate
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : milling, sieving, (micronisation) 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

4. Non-Compliant Other Activities - Active Substances :
The NCR applies to all active substances of the site. List of other active substances manufactured on the site (as communicated by the company - non exhaustive list): Ambroxol Hydrochloride, Azithromycin, Chloramphenicol, Chloramphenicol Palmitate, Ciprofloxacin HCl, Clarithromycin, Erythromycin, Erythromycin Estolate, Erythromycin Propionate, Erythromycin Stearate, Losartan Potassium, Piperaquine phosphate, Pyrazinamide, Roxythromycin, Sulfadoxine.

Part 3

1. Nature of non-compliance:

Overall, 24 deficiencies were observed during the inspection, 1 Critical and 2 Major deficiencies: * * * [Critical 1] No transfer of information to the user of the active substance as regards to the original manufacturers of the active substances only micronized at the site (i.e. manufacturer name, original batch number and COA) and exported to Europe or that may be sold to distributors exporting to Europe. The following active substances were micronized from other sources (as communicated by the company - may not be exhaustive): Azithromycin, Chloramphenicol, Chloramphenicol Palmitate, Ciprofloxacin HCl, Clarithromycin, Piperaquine phosphate, Roxithromycin and Sulfadoxine. Moreover, a non EU-GMP compliant source for Azithromycin (NCF/010/RO, Hebei Dongfang Pharmaceutical Co., Ltd, China) was micronized and directly exported to Europe under the manufacturer name Anuh Pharma. * * * [Major 1] Deficiencies in documentation management. Several documents were found within a pile of rubble on the other side of a wall. These included an original batch repacking record which should have been placed under retention and a large number of purchase orders dated from 2013 for active substances, notably Azithromycin, Chloramphenicol, Chloramphenicol Palmitate, Roxithromycin and Ciprofloxacin HCl. * * * [Major 2] Deficiencies in process validation. No validation data was available for the blending of micronized batches. No cleaning validation was available for one air jet mill used for micronization. No supporting data for the reduced testing of the recovered Ethyl Acetate solvent was available.

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. IT /E/GMP/9/2013
Using QRM principles, consideration of withdrawal of current valid EU GMP certificate issued by the Agencia Italiana del Farmaco (IT/E/GMP/9/2013).

Requested Variation of the marketing authorisation(s)
Using QRM principles, use of an alternate manufacturer should be considered.

Recall of batches already released
Using QRM principles, recall of products should be considered. The risk / benefit ratio for the patients has to be assessed by NCAs to prevent shortage of critical products.

Prohibition of supply
The site has been issued a statement of non compliance and active substances manufactured by the site should not be used for the manufacturing of medicinal products. The risk / benefit ratio for the patients has to be assessed by NCAs to prevent shortage of critical products.

Suspension or voiding of CEP (action to be taken by EDQM)
This inspection was carried out as part of the EDQM inspection programme. The impact of this NCR on the CEPs is to be decided by the EDQM. The concerned CEPs are : CEP 2007-235 (Erythromycin Ethylsuccinate), CEP 2005-059 (Pyrazinamide), CEP 2005-205 (Erythromycin).

Additional comments
The findings reveal a critical non-compliance of the quality system of the company as a whole. Moreover, due to the severe lack of transparency of the company regarding its manufacturing activities, there is no assurance as regards to the origin of every batch of active substances claimed to have been manufactured by the company at the Boisar site. Consequently, it is considered that the identified risks are applicable to all active substances manufactured at the site.

2016-03-24

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

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Confidential
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