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保存年限：

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速別：普通件
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(A21020000I106110100100-1.pdf)

主旨：有關巴西原料藥廠「Antibioticos Do Brasil Ltda」（廠址：Rod. Prof. Zeferino Vaz SP 332, Km 135, Bairro Itapavussu, Cosmopolis, San Paolo, 13150-000, Brazil）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、義大利衛生主管機關Italian Medicines Agency（IMA）於105年12月16日查核旨揭原料藥廠，判定嚴重違反GMP，並於106年1月5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)旨揭原料藥廠「BC-3 Building」製造之所有原料藥及Bulk產品應暫停出貨。

(二)擬凍結原料藥「Ceftazidime Pentahydrate with Sodium Carbonate for Injection Sterile」之CEP證明文件（RO-CEP 2010-026-Rev 01）。

三、鑑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，並應依說明段二（一）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

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Italian Medicines Agency

Report No: *IT/GMP/E/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: ***ANTIBIOTICOS DO BRASIL LTDA***
Site address: ***Rod. Prof. Zeferino Vaz ¿ SP 332, Km 135, Bairro Itapavussu, Cosmopolis, San Paolo, 13150-000, Brazil***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-12-16*** , it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC
- 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

Human Medicinal Products

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;	
1.1	**Sterile products**
	1.1.1 Aseptically prepared (processing operations for the following dosage forms) 1.1.1.6 Other: aseptic blending of powders(en) Special Requirements 1 B-lactam Antibiotics
	1.1.3 Batch certification
1.4	**Other products or manufacturing activity**
	1.4.2 Sterilisation of active substance/ excipients/ finished product 1.4.2.1 Filtration
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility *1.6.2 Microbiological: non-sterility* *1.6.3 Chemical/Physical*

Manufacture of active substance. Names of substances subject to non-compliant :
CEPHALEXIN SODIUM STERILE(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES Active Substance : CEPHALEXIN SODIUM STERILE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates 3.1.3 Salt formation / Purification steps : Crystallisation
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Drying, milling 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 3.6.3 Microbiological testing including sterility testing

Any restrictions related to the scope of this statement :

Building	Room	Line/equipment	QC testing	Products
BC-3				***confidential***

Part 3

1. Nature of non-compliance:

Four critical and seven major deficiencies have been found. Critical dficieneies: C1. During the inspection tour into the classified production area (ancillary rooms for crystallisation area B class) it was noted that ABL failed to ensure a good level of maintenance and cleaning of the area. In addition, ABL showed a poor level of training, low knowledge and awareness of GMP, lack of supervisors control and some non-authorised and fraudulent activities that were stopped before the inspectors came into the rooms number 251-252 (D and C class). C2. Regarding the environmental monitoring of crystallisation area (B class), it was noted that the principles stated in the Annex A of the EU GMP were not followed and no additional environmental controls were applied to ensure a good pharmaceutical environmental during the production in the sterile area. C3. ABL did not implement a robust pharmaceutical quality management system. While ABL has many SOPs in place, during this inspection it was noted that procedures were not being robustly followed and related actions were not fully investigated, risk assessed, justified, and fully documented. During the inspection, it was noted that anomalous events had not been appropriately investigated and documented as the following example for APQR, handling of deviations and investigations, handling of OOT and CAPA evaluation. C4.ABL failed to establish and maintain documents to record correctly and trace back all activities and to ensure appropriate quality documentation that form part of the quality management system. Major deficiencies: M1. During the inspection, ABL replied inconsistently in some situations and interviewed personnel was not able to give/show promptly the correct reply/document. M2. The laboratory failed to establish and maintain a comprehensive and robust policy, procedures and controls to ensure the reliability and integrity of analytical data. M3. The design of the QC microbiological laboratory failed to maintain a rationale material flow in order to prevent a potential contamination during the testing performance. M4. Several standard operating procedures SOPs and working instructions were found inadequate as they did not include the operational details or were lacking in instructions. M5. There were no provisions to prevent a potential contamination/cross-contamination for the activities performed in the room number 203 -dispensing and sampling. M6. ABL failed to ensure that the quality of fluids (PW and Nitrogen) used in production and in contact with the product were correctly monitored and analysed. M7. Regarding the training procedure and annual training programme, it was noted that a specific training on European GMP (Eudralex vol. 4) was not scheduled; neither a gap analysis between Brazilian and European GMP was performed in order to verify the overlapping of the two guidelines.

Action taken/proposed by the NCA

Prohibition of supply
For all drug substances and bulk drug products manufactured in BC-3.

Suspension or voiding of CEP (action to be taken by EDQM)
R0-CEP 2010-026-Rev 01 - Ceftazidime pentahydrate with sodium carbonate for injection Sterile

Additional comments
Due to the number and nature of raised deficiencies, a new GMP inspection is needed, even if a CAPA plan is submitted, in order to assess effective removal of deficiencies.

2017-01-05

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

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