檔　　號:
保存年限:

衛生福利部食品藥物管理署 函

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發文日期：中華民國111年11月14日
發文字號：FDA品字第1111107528號
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 (A21020000I_1111107528_doc1_Attach1.pdf)

主旨：義大利原料藥廠「Trifarma S.p.A.（廠址：Via Pavese 2, Rozzano, 20089, Italy」經國外官方判定違反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 (AIFA)於111年5月24日至27日查核旨揭原料藥廠，判定違反GMP，並於111年10月26日發布「STATEMENT OF NON-COMPLIANCE WITH GMP」。

二、鑑於上述原料藥廠之製造品質恐無法符合GMP之要求，導致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國產及輸台製劑產品是否使用上述原料藥廠所生產原料藥，並應依風險管理原則執行相關後續處置。

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、台灣藥品行銷暨管理協會、台灣製藥工業同業公會、中華民國學名藥協會、中華民國製藥發展協會
副本：電子公文交換章 2022/11/15 14:24:45

Italian Medicines Agency

Report No: ***IT/NCR/API/1/2022***

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: ***Trifarma S.p.A.***
Site address: ***Via Pavese 2, Rozzano, 20089, Italy***
OMS Organisation Id. / OMS Location Id.: ***ORG-100013844*** / ***LOC-100019765***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2022-05-27***, 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 1.4.1.3 Other: active substance(en)

Manufacture of active substance. Names of substances subject to non-compliant:
MILRINONE(en)
FLUPHENAZINE HYDROCHLORIDE(en)
FLUPHENAZINE DECANOATE(en)
PROCHLORPERAZINE(en)
PROCHLORPERAZINE MALEATE(en)
PROCHLORPERAZINE EDISYLATE(en)
THIORIDAZINE HYDROCHLORIDE(en)
TRIFLUOPERAZINE HYDROCHLORIDE(en)
PERPHENAZINE(en)
PERPHENAZINE DECANOATE(en)
CLINDAMYCIN PHOSPHATE(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance:MILRINONE

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: crystallisation
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: drying 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

Active Substance:FLUPHENAZINE HYDROCHLORIDE

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: salt formation, crystallisation
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

Active Substance:FLUPHENAZINE DECANOATE

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: crystallisation 3.1.4 Other: desalification
3.5	**General Finishing Steps**
	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

Active Substance:PROCHLORPERAZINE

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: crystallisation 3.1.4 Other: desalification
3.5	**General Finishing Steps**
	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

Active Substance:PROCHLORPERAZINE MALEATE

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: crystallisation, salt formation
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

Active Substance:PROCHLORPERAZINE EDISYLATE

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: crystallisation, salt formation
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: drying 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

Active Substance:THIORIDAZINE HYDROCHLORIDE

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:

	salt formation, crystallisation
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

Active Substance:TRIFLUOPERAZINE HYDROCHLORIDE

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: salt formation, crystallisation
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

Active Substance:PERPHENAZINE

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: crystallisation
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
Active Substance:PERPHENAZINE DECANOATE	
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: crystallisation 3.1.4 Other: desalification
3.5	**General Finishing Steps**
	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
Active Substance:CLINDAMYCIN PHOSPHATE	
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: crystallisation
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: drying 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:
Importation of: Clindamycin Hydrochloride (confidential)

Part 3

1.Nature of non-compliance:
13 ‘Major’ and 1 ‘Other’ deficiencies were found during the inspection. The ‘Major’ deficiencies were related to inadequate pharmaceutical quality system, building and equipment maintenance. In particular: 1) unauthorized production and equipment records have been found during the inspection; the records, found in the production facilities, were non GMP documentation reporting information about manufacturing activities and equipment use/maintenance not recorded in the GMP documentation such as Batch record nor equipment registers. 2) lack in buildings and equipment maintenance and use and cleaning operations; most of the facilities have been found dirty, not adequately designed for the intended use and with equipment not adequately cleaned nor maintained. Other relevant findings have been found in material management, utilities, documentation management. AIFA suspended the manufacturing site, as per Company’s request. Recall from the market was not put in place. Medicinal products containing the active substances manufactured by Trifarma are considered critical; shortage of the medicinal products is considered a real risk.
Action taken/proposed by the NCA **Withdrawal, of current valid GMP certificate No. IT-API/81/H/2019** Withdrawal of current valid GMP certificate n. IT-API/81/H/2019; issue date 2019.06.05 **Requested Variationof the marketing authorisation(s)** Each involved NCA should evaluate, following assessment conducted in conjunction with MAHs, if a recall of medicinal product is needed. **Prohibition of supply** Evaluation should take into account if there are alternative suppliers and potential risk of shortage. Based on the evaluation of the retested results of the batches already released at the time of the AIFA inspection but not shipped yet and information provided by the Company, considering the real risk of shortage of the critical medicinal products containing the active substances manufactured by Trifarma, AIFA will authorised the ditribution. **Others** This supplier should not be approved in any new / on going applications. Each involved NCA should evaluate if the supplier should be removed from existing MAs. On 29 September, Company submitted a request for restoring the manufacturing activities at the site. AIFA’s evalution is on going.

2022-10-26

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

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Confidential
Italian Medicines Agency
Tel:***Confidential***
Fax:***Confidential***