National Agency For The Safety Of Medicine And Health Products

Report No: ***2026_NCR_MEDBIO_003***

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 France confirms the following:
The manufacturer: ***Bio-Thera Solutions Ltd.***
Site address: ***155 Yaotianhe Street Huangpu District, Guangzhou, Guangdong, 511356, China***
OMS Organisation Id. / OMS Location Id.: ***ORG-100013490*** / ***LOC-100050256***
DUNS Number: ***52-968-7318***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2026-02-12***, 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 (EU) 2017/1572

Note to receiving authorities: Please contact the issuing authority within 20 working days in case there are critical(2) medicinal products potentially affected by this statement.
Manufacturing Authorisation Holders directly affected by this statement have failed to comply with their obligations under Art. 46 of Directive 2001/83/EC or Art. 93(1)(j) to (l) of Regulation (EU) 2019/6 and as a consequence the Qualified Person referred to in Art. 48 of Directive 2001/83/EC and Art. 97(1) of Regulation (EU) 2019/6 is unable to perform the batch certification referred to in Art. 51 of Directive 2001/83/EC and Art. 97 (6) and (7) of Regulation (EU) 2019/6.
In exceptional circumstances there may be no objection to the Qualified Person certifying affected batches thereby allowing their release provided all of the following conditions are fulfilled:

1. Batch certification is performed in order to maintain supply of critical medicinal products only.
2. A documented risk assessment has been performed by, or on behalf of, the Qualified Person and additional actions have been implemented by the manufacturing and/or batch release site to mitigate the risks posed by the non-compliance. Note: Repeated testing alone is not normally sufficient risk mitigation but, together with other actions, can form part of a strategy commensurate with the nature and the level of risk.
3. A thorough risk-benefit evaluation has been performed for the acceptance of risk and a report prepared that takes full account of the nature of the non-compliance with the involvement of:
   - The Manufacturing Authorisation Holder and the Qualified Person of the site responsible for batch certification.
   - The manufacturing site subject to this Statement of Non-Compliance, if different from the above.

- The relevant Marketing Authorisation Holder(s).

The report has been shared with the National Competent Authorities of the countries in which distribution of the affected batches is anticipated and that any comments from those authorities have been taken into account.

4. Written confirmation has been obtained from the National Competent Authorities in whose territories the affected batches are intended to be distributed that the product is considered critical on its territory, and that there is no objection to distribution.
5. The Supervisory Authority has been informed, if different from the above, and it has not suspended or revoked the relevant Manufacturing Authorisation.
6. The affected Marketing Authorisations have not been revoked or suspended.
7. Any further conditions imposed by the Supervisory Authority and other involved National Competent Authorities are met.

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[1] *The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and Art. 94(2) of Regulation (EU) 2019/6, as amended, is also applicable to importers.*

[2] *See Appendix 3 of the relevant procedure in the Compilation of Union Procedures.*

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) 1.1.1.4 Small volume liquids
1.3	**Biological medicinal products (list of product types)**
	1.3.1 Biological medicinal products (list of product types) 1.3.1.5 Biotechnology products
1.5	**Packaging**
	1.5.2 Secondary packaging
1.6	**Quality control testing**
	1.6.1 Microbiological: sterility *1.6.2 Microbiological: non-sterility* *1.6.3 Chemical/Physical* *1.6.4 Biological*

Clarifying remarks (for public users)

With regard to finished products, the inspection scope was limited to the manufacture of the biosimilar products : - Usymro® 45 mg and 90 mg, solution for injection, Usymro® 130 mg, concentrate for solution for infusion (vial and pre-filled syringe presentations); - Avzivi® 25 mg/mL concentrate for solution for infusion (vial presentation); - Tofidence® 20 mg/mL concentrate for solution for infusion (vial presentation); - Gotenfia® 50 mg and 100 mg solution for injection (pre-filled syringe presentation). Signatory: Mr Guillaume Renaud - Inspection division. The ANSM does not issue hard copy of this statement.

Part 3

1.Nature of non-compliance:

This NCR is limited to the drug product manufacturing activities related to the 4 products: - Usymro® (Ustekinumab) 45 mg and 90 mg, solution for injection and Usymro® (Ustekinumab) 130 mg, concentrate for solution for infusion (vial and pre-filled syringe presentations); - Avzivi® (Bevacizumab) 25 mg/mL concentrate for solution for infusion (vial presentation); - Tofidence® (Tocilizumab) 20 mg/mL concentrate for solution for infusion (vial presentation); - Gotenfia® (Golimumab) 50 mg and 100 mg solution for injection (pre-filled syringe presentation). The inspection raised 33 deficiencies including 1 critical deficiency and 8 major deficiencies related to drug product manufacturing activities. One critical deficiency was raised: 1) Failure to investigate and assess product impact in the deviations including deviations related to Aseptic Process Simulation (APS) failure and environmental monitoring excursions in grade A/B cleanrooms. Eight major deficiencies were raised: 1) Failure to have efficient cleaning and disinfection practices of cleanrooms, as well as material transfer processes to grade A/B areas, by using practices that were not conducive to minimizing microbial contamination; 2) Failure to have suitable manual visual inspection process of filled units by deviating from Eur. Pharmacopeia requirements and from qualification data of manual inspection tables; 3) Failure to requalify cleanroom for the prefilled syringe filling room in accordance with Annex 1 of EU GMP; 4) Failure to implement cleanroom environmental monitoring program fully in accordance with Annex 1 of EU GMP; 5) Failure to adequately manage particle contamination on 200 L single-use storage bags (used during vial filling of Avzivi® and Tofidence®) by modifying the manufacturing process to include a 3 µm filter after the final sterilizing filtration 0,22 µm; 6) Failure to adequately define the aseptic interventions for the annual requalification of operators of filling lines as well as acceptance criteria during the initial qualification of the QC employees for APS reading; 7) Failure to manage computerized systems in the QC lab in accordance with Annex 11 of EU GMPs requirements; 8) Failure to establish approved quality agreements with Marketing Authorization Holders and Importers.

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. 2024_HPF_PT_003_NA

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Prohibition of supply

No batch of the 4 products manufactured prior to the issuance of this NCR and manufactured while this NCR is in force should be supplied to Europe.

Additional comments

A follow-up GMP inspection is required in order to ensure that the entire CAPA plan has been adequately implemented.

2026-06-12

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

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