French National Agency for Medicines and Health Products Safety

Report No: ***19MPP051NCR01***

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

The competent authority of France confirms the following:
The manufacturer: ***Jiangxi Dongfeng Pharmaceutical Co., Ltd***
Site address: ***1 Dongfeng Road, Leping Industrial Park, Leping City, Jiangxi Province, 333300, China***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2019-06-27***, 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 51 of Directive 2001/82/EC.

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

Veterinary 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;

1.4	**Other products or manufacturing activity**
	1.4.2 Sterilisation of active substance/ excipients/ finished product 1.4.2.1 Filtration Special Requirements 1 B-lactam Antibiotics

Manufacture of active substance. Names of substances subject to non-compliant:
BENZYLPENICILLIN PROCAINE +1% LECITHIN (STERILE)(en)
BENZYLPENICILLIN BENZATHINE +1% LECITHIN (STERILE)(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance:BENZYLPENICILLIN PROCAINE +1% LECITHIN (STERILE)

3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps: Crystallization, Filtration
3.4	**Manufacture of sterile Active Substance**
	3.4.1 Aseptically prepared
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: Drying, Micronizing 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

Active Substance:BENZYLPENICILLIN BENZATHINE +1% LECITHIN (STERILE)

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3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.3 Microbiological testing including sterility testing

Clarifying remarks (for public users)

Veterinary use / Signatory : Mr Guillaume Renaud, Deputy Director of inspection division --- The ANSM does not issue hard copies of good practices certificates

Part 3

1.Nature of non-compliance:
Overall,28 deficiencies were observed during the inspection, including 4 Major deficiencies: [Major 1] Inapropriate frequency for the microbiological and chemical testing of the steam used for equipment sterilization; [Major 2] Risks of contamination in the manufacturing area of sterile APIs; [Major 3] Failure in the sterilization process and in the microbiological monitoring of the RABS (Restricted Access Barrier System); [Major 4] Failure for the temperature monitoring process during sterilization run for several equipment; [Major 5] Failure for the evaluation and the management of a supplier of the sterile LPDE (Low Density Polyethylene) bags used for the packaging of sterile APIs; [Major 6] Risks of loss of sterility of sterile APIs during the filling process; [Major 7] Use of reusable drums not under control; [Major 8] Failure for the aseptic process simulation test; [Major 9] Failure for the recovery process of solvents.
Action taken/proposed by the NCA **Recall of batches already released** A recall of products should be considered using QRM principles. **Prohibition of supply** After issuance of the non-compliance report and as long as it remains active, the site should not be named in any new MAs or used in drug compounding activities.
Additional comments The existence of MAs or MA variations referencing an active substance manufactured by Jiangxi Dongfeng Pharmaceutical Co., Ltd has to be verified. Where such a MA exists, the removal of the site from the MA should be considered using quality risk management (QRM) principles.

2019-10-17

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

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