

Health And Youth Care Inspectorate

Report No: *NL/H 26/2008484D*

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 manufacturer¹

Part 1

Issued following an inspection in accordance with
Art. 63 of Regulation (EU) 536/2014 as amended

The competent authority of Netherlands confirms the following:

The manufacturer: *Het Nederlands Kanker Instituut-Antoni van Leeuwenhoek Ziekenhuis Stichting*

Site address: *Plesmanlaan 121, Amsterdam, 1066 CX, Netherlands*

OMS Organisation Id. / OMS Location Id.: *ORG-100033850 / LOC-100053279*

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on **2026-04-23**, it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- Commission Delegated Regulation (EU) 2017/1569

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.

¹The 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.

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

Part 2

Human Investigational 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
	<i>1.1.1 Aseptically prepared (processing operations for the following dosage forms)</i> 1.1.1.6 Other: cell therapy products and gene therapy products(en)
	<i>1.1.3 Batch certification</i>
1.2	Non-sterile products
	<i>1.2.2 Batch certification</i>
1.3	Biological medicinal products (list of product types)
	<i>1.3.1 Biological medicinal products (list of product types)</i> 1.3.1.3 Cell therapy products Special Requirements 3 Live Cells 1.3.1.4 Gene therapy products Special Requirements 3 Live Cells 1.3.1.5 Biotechnology products Special Requirements 3 Live Cells
	<i>1.3.2 Batch Certification (list of product types)</i> 1.3.2.3 Cell therapy products 1.3.2.4 Gene therapy products 1.3.2.5 Biotechnology products
1.5	Packaging
	<i>1.5.2 Secondary packaging</i>
1.6	Quality control testing
	<i>1.6.1 Microbiological: sterility</i> <i>1.6.2 Microbiological: non-sterility</i> <i>1.6.3 Chemical/Physical</i> <i>1.6.4 Biological</i>

Clarifying remarks (for public users)

ad 1.1.3 and 1.2.2: Batch certification of human investigational medicinal products, prepared at location :Louwesweg 6 as well as location Plesmanlaan 121 in Amsterdam is performed at location Plesmanlaan 121 in Amsterdam; ad 1.6.4 concerns endotoxin tests and flowcytometry.

Part 3

1. Nature of non-compliance:

The GMP inspection has been performed on February 10–12, 2026 and April 22-23, 2026. This manufacturer, a hospital pharmacy, is producing multiple type of products: medicinal products for human use with a marketing authorization, advanced therapy medicinal products (ATMPs, investigational) and human investigational medicines. It concerns sterile production of registered products and ATMPs and non-sterile production of registered products. In addition, the activities of investigational medicinal products are manufacturing of tablets/capsules, and relabeling and repackaging. All of the clinical studies are performed in the Netherlands, except one study is performed in Europe (M22BOL EU CT 2023-505039-11-00). The outcome of the inspection was GMP non-compliant, which is based on one (1) critical deficiency, seven (7) major deficiencies and fourteen (14) other deficiencies. In summary the main inspection findings were as follows: Critical deficiency: 1) The execution of the Out-of-Specification (OOS) process is inadequate. In practice, multiple batches of registered finished products were released even though they did not comply with the specified limits for moisture content or assay. An Advanced Therapy Medicinal Product (ATMP) was released despite a failed sterility test which was performed as an in-process control. In addition, the procedure for OOS is not unambiguous and can lead to batch certification and release without thorough investigation of sufficient justification. Major deficiencies: 1) The control of aseptic practices for both the registered product and the ATMP manufacturing process is insufficient e.g. Annex1 gap assessment and the contamination control strategy are incomplete. Regarding ATMP production multiple aspects are not under control. 2) Aseptic process simulation is inadequate for both the registered product and the ATMP process, including the additional media fill. 3) The design, investigation and trending of microbiological test results are insufficient for example multiple microbial exceedances on the hands of the operators in class A handling the ATMP product. 4) Operator behaviour in the cleanroom and gowning procedures for Grade B areas are inadequate. 5) The Pharmaceutical Quality System (PQS) is insufficient. This is shown by deficiencies identified in the management of deviations, CAPAs, changes, complaints, self-inspections, and the Product Quality Reviews (PQRs) that were assessed. 6) The approach to Computerized System Validation (CSV) and data integrity is inadequate. 7) Good Documentation Practices (GDocP) are not sufficiently adhered to, as demonstrated for example by the backlog of revisions for multiple documents. In conclusion: the impact of the GMP non-compliance on registered products, ATMPs and most of the investigational medicinal products is exclusively national, except for one clinical study (EU CT 2023-505039-11-00)(see paragraph: suspension of clinical trials).

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. NL/H 24/2051740C, NL/H 24/2051740D

Including the GMP certificates of Louwesweg 6, Amsterdam e.g. NL/H 24/2051740A and NL/H 24/2051740B. A re-inspection will be performed on the basis of the company's plan of action to address the deficiencies (currently not scheduled yet). After a positive result following the re-inspection a new GMP certificate will be issued and this non-compliance statement will be withdrawn.

Suspension of clinical trials

For the EU only one product is impacted: M22BOL study (EU CT 2023-505039-11-00). The activities are relabeling and repackaging of DS-8201a (trastuzumab deruxtecan). All the other products are solely present on the Dutch market. Impact: The impact of the inspection findings for EU CT 2023-505039-11-00, where a registered product will be relabeled and repacked by NKI/AVL, will be limited. This is an existing and released medicinal product. The critical shortcoming plus the four major shortcomings regarding sterile manufacturing and aseptic production do not affect this

investigational medicinal product. However, major shortcomings regarding the Quality Management System, Computer System Validation and Good Documentation practice could affect this investigational medicinal product. Recommendations: Up to this moment, four patients out of the expected total amount of 72 patients have been treated since the start of the clinical trial May, 2, 2024. Those four patients were treated in the Netherlands. It is up to the concerned Member States to make a decision regarding their market taking into account the legal frameworks.

Additional comments

No need for a teleconference since the impact is restricted.

Products manufactured at site, if known	Products	EudraCT/CTIS nos.
Investigational Medicinal Products	DS-8201a (trastuzumab deruxtecan)	EU CT 2023-505039-11-00

2026-10-07

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

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