EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Statement of non-compliance with GMP

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(LETTERHEAD OF COMPETENT AUTHORITY)

Report No: _ _ _/_ _ _/_ __/_ _

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 *(Human Medicines)*, Art. 94(2) of Regulation (EU) 2019/6 *(Veterinary Medicines)* or Article 63(4) of Regulation (EU) No 536/2014 *(Investigational Medicinal Products)*.*

The competent authority of..... *[Member State]* confirms the following:

The manufacturer: .....

Manufacturer's alternative name: .....

Site address .....

Additional details on units inspected:

.....

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ...../...../.....*[date]*, 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 *(GMP for Human Medicines)*/ Commission Delegated Regulation (EU) 2017/1569 (*GMP for Investigational Human Medicines*)/Directive 91/412/EEC *(GMP for Veterinary Medicines)*/ the principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC *(GMP for Active Substances in Human Medicines)* / Article 93(2) of Regulation (EU) 2019/6 *(GMP for Active Substances in Veterinary Medicines)* / an appropriate level of GMP as referred to in Article 46(f) of Directive 2001/83/EC *(GMP for Active Substances in Human Medicines)** and Article 93(1) (j) to (l) of Regulation (EU) 2019/6 *(GMP for Active Substances in Veterinary Medicines*)

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.

[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

Manufacturing Authorisation Holders directly affected by this statement have failed to comply with their obligations under Art. 46fof 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:

   Figure: 1. The Manufacturing Authorisation Holder and the Qualified Person of the site responsible for batch certification

   Figure: 2. The manufacturing site subject to this Statement of Non-Compliance, if different from the above

   Figure: 3. 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. **Note: Responsibility for batch certification remains with the Qualified Person**.
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

Part 2

In the sections below, highlight the manufacturer's activities that the NCS is relevant to.

- ☐ Human Medicinal Products*
- ☐ Veterinary Medicinal Products*
- ☐ Human Investigational Medicinal Products*

1 NON-COMPLIANT MANUFACTURING OPERATIONS- MEDICINAL PRODUCTS*	
1.1	**Sterile Products**
	1.1.1 Aseptically prepared (processing operations for the following dosage forms) 1.1.1.1 Large volume liquids 1.1.1.2 Lyophilisates 1.1.1.3 Semi-solids 1.1.1.4 Small volume liquids 1.1.1.5 Solids and implants 1.1.1.6 Other <free text>
	1.1.2 Terminally sterilised (processing operations for the following dosage forms) 1.1.2.1 Large volume liquids 1.1.2.2 Semi-solids 1.1.2.3 Small volume liquids 1.1.2.4 Solids and implants 1.1.2.5 Other <free text>
	1.1.3 Batch certification
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.1 Capsules, hard shell 1.2.1.2 Capsules, soft shell 1.2.1.3 Chewing gums 1.2.1.4 Impregnated matrices 1.2.1.5 Liquids for external use 1.2.1.6 Liquids for internal use 1.2.1.7 Medicinal gases 1.2.1.8 Other solid dosage forms 1.2.1.9 Pressurised preparations 1.2.1.10 Radionuclide generators 1.2.1.11 Semi-solids 1.2.1.12 Suppositories 1.2.1.13 Tablets 1.2.1.14 Transdermal patches 1.2.1.15 Intraruminal devices 1.2.1.16 Veterinary premixes 1.2.1.17 Other <free text>
	1.2.2 Batch certification
1.3	**Biological medicinal products**

	1.3.1 Biological medicinal products 1.3.1.1 Blood products 1.3.1.2 Immunological products 1.3.1.3 Cell therapy products 1.3.1.4 Gene therapy products 1.3.1.5 Biotechnology products 1.3.1.6 Human or animal extracted products 1.3.1.7 Tissue engineered products 1.3.1.8 Other <free text>
	1.3.2 Batch certification (list of product types) 1.3.2.1 Blood products 1.3.2.2 Immunological products 1.3.2.3 Cell therapy products 1.3.2.4 Gene therapy products 1.3.2.5 Biotechnology products 1.3.2.6 Human or animal extracted products 1.3.2.7 Tissue engineered products 1.3.2.8 Other <free text>
1.4	**Other products or manufacturing activity**
	1.4.1 Manufacture of: 1.4.1.1 Herbal products 1.4.1.2 Homoeopathic products 1.4.1.3 Other <free text>
	1.4.2 Sterilisation of active substances/excipients/finished product: 1.4.2.1 Filtration 1.4.2.2 Dry heat 1.4.2.3 Moist heat 1.4.2.4 Chemical 1.4.2.5 Gamma irradiation 1.4.2.6 Electron beam
	1.4.3 Others <free text>
1.5	**Packaging**
	1.5.1 Primary packing 1.5.1.1 Capsules, hard shell 1.5.1.2 Capsules, soft shell 1.5.1.3 Chewing gums 1.5.1.4 Impregnated matrices 1.5.1.5 Liquids for external use 1.5.1.6 Liquids for internal use 1.5.1.7 Medicinal gases 1.5.1.8 Other solid dosage forms 1.5.1.9 Pressurised preparations 1.5.1.10 Radionuclide generators 1.5.1.11 Semi-solids 1.5.1.12 Suppositories 1.5.1.13 Tablets 1.5.1.14 Transdermal patches 1.5.1.15 Intraruminal devices 1.5.1.16 Veterinary premixes 1.5.1.17 Other <free text>
	1.5.2 Secondary packing
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

2 NON-COMPLIANT IMPORTATION OPERATIONS*	
2.1	**Quality control testing of imported medicinal products**
	2.1.1 Microbiological: sterility
	2.1.2 Microbiological: non-sterility
	2.1.3 Chemical/Physical
	2.1.4 Biological
2.2	**Batch certification of imported medicinal products**
	2.2.1 *Sterile Products* 2.2.1.1 Aseptically prepared 2.2.1.2 Terminally sterilised
	2.2.2 Non-sterile products
	2.2.3 Biological medicinal products 2.2.3.1 Blood products 2.2.3.2 Immunological products 2.2.3.3 Cell therapy products 2.2.3.4 Gene therapy products 2.2.3.5 Biotechnology products 2.2.3.6 Human or animal extracted products 2.2.3.7 Tissue engineered products 2.2.3.8 Other <free text>
2.3	**Other importation activities**
	2.3.1 Site of physical importation
	2.3.2 Importation of intermediate which undergoes further processing
	2.3.3 Biological active substance
	2.3.4 Other <free text>

Any restrictions or clarifying remarks related to the scope of this statement*:

Clarification should be provided as to why the scope of NCS is limited, such as non-compliance of partial site activities (e.g. activities regarding sterility assurance are non-compliant but non sterile manufacturing activities are deemed compliant); or targeted inspection (e.g. sterile products inspection at a site manufacturing both sterile and non-sterile dosage forms),

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.....

3 MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES Active Substance(s):	
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: <free text> (e.g. crystallisation)* *3.1.4 Other <free text>*
3.2	**Extraction of Active Substance from Natural Sources**
	3.2.1 Extraction of substance from plant source *3.2.2 Extraction of substance from animal source* *3.2.3 Extraction of substance from human source* *3.2.4 Extraction of substance from mineral source* *3.2.5 Modification of extracted substance <specify source 1,2,3,4>* *3.2.6 Purification of extracted substance <specify source 1,2,3,4 >* *3.2.7 Other <free text>*
3.3	**Manufacture of Active Substance using Biological Processes**
	3.3.1 Fermentation *3.3.2 Cell Culture <specify cell type> (e.g. mammalian / bacterial)* *3.3.3 Isolation / Purification* *3.3.4 Modification* *3.3.5 Other <free text>*
3.4	**Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)**
	3.4.1 Aseptically prepared *3.4.2 Terminally sterilised*
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps < specify > (e.g. drying, milling / micronisation, sieving) *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)* *3.5.4 Other <free text> (for operations not described above)*
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing *3.6.2 Microbiological testing (excluding sterility testing)* *3.6.3 Microbiological testing (including sterility testing)* *3.6.4 Biological Testing*

4. OTHER ACTIVITIES- ACTIVE SUBSTANCES

<*free text*>

Any restrictions or clarifying remarks related to the scope of this statement*:
Clarification should be provided as to why the scope of NCS is limited, e.g. non-compliance of partial site activities; targeted inspection

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Part 3

1. Nature of non-compliance

<free text>

EudraGMDP allows only 999 characters

State a brief summary of the critical and major deficiency / deficiencies that have led to the NCS being issued, e.g:

> *"Failure to manage GMP changes, risks of cross contamination between hazardous products, failure to control sterilisation processes"*

GMP deficiencies which did not influence the decision to issue the NCS should not be described.

Keep the description factual, concise and based on the non-conformance(s) reported to the manufacturer.

Consider possible interpretation issues when describing deficiencies and making recommendations.

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2. Action taken/proposed by the NCA

EudraGMDP requires a text entry for any 'checked boxes'. Any text entry requires the relevant box to be checked.

☐ Suspension/variation/revocation* of the manufacturing authorisation No..... in full/in part*

<free text> *State any proposed (or taken) action on the manufacturing authorisation. If so, state the action and timescale involved.* .....

.....

☐ Restriction of current valid GMP certificate No. .....

<free text> *State the current GMP certificate reference and if any restriction / withdrawal is proposed or already actioned, with explanation (e.g. issued for other compliant activities).* .....

In most cases, NCS becomes effective from the date of publication on EudraGMDP. If the NCA recommends that the NCS be applied retrospectively to batches previously manufactured (but not yet QP certified or released to the market), this should be clearly stated, with rationale.

.....

☐ Suspension/revocation/requested variation/ refusal to grant * of Marketing Authorisation(s)

<free text> *The issuing authority may make recommendations for action against affected marketing authorisations. This should be described in the context of the impact of GMP deficiency on product quality or safety. Recommendations should be stated in a manner which permits flexibility in decision-making at national and Union level, taking into account product criticality.*

Avoid statements such as "recommendation that MA should be suspended". Instead consider "action against affected MAs should be considered where potential quality defect has greater impact to public health than supply restriction in affected Member State(s)". Refer to guidance on Regulatory Risk Assessment for advice.

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☐ Recall of batches already released (separate Rapid Alert to follow)

<free text> *State if there is evidence or significant risk of defective product on the market. Is recall recommended or is it not considered necessary? Where possible, agree text with the authority leading quality defect assessments.*

Recommendations to other Member States should usually be limited to 'consideration of recall, following NCA assessment of potential quality defect vs. supply restriction'. .....

.....

☐ Prohibition of supply

<free text> *Are any restrictions on supply recommended whilst the NCS is in force? For example, no further batches to be supplied to the market.* .....

.....

☐ Suspension or voiding of CEP (action to be taken by EDQM)

<free text> *If action against a CEP may be considered, liaise with EDQM to agree the wording for this section.*
.....

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☐ Suspension of clinical trials

<free text> *The issuing authority may make recommendations for suspension of clinical trials. This should be described in the context of the impact of GMP deficiency on investigational product quality or safety, or trial data validity. Recommendations should be stated in a manner which permits flexibility in decision-making at national and Union level, taking into account clinical trial criticality.*

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☐ Others <free text>

<free text> *State any other relevant information that is not already covered, e.g. information on supply of unauthorised products under Art 5(1)*.....

.....

3. Additional comments

<free text> *EudraGMDP allows only 999 characters. Use this field to add further explanation to support compliance or product quality risks related to the GMP deficiencies. Also use to provide rationale for any NCS scope restrictions.*

....

Teleconference Date		**Teleconference Time (CET)**		**Dial in no.**	
Products manufactured at site, if known	**Product**	**Dosage Form**	**Reference Member State, National or EMEA**		
Human medicinal product(s)					
Veterinary medicinal product(s)					
Investigational medicinal product(s)	**EudraCT/CTIS nos.**				

Guidance: where complete product lists and/or EudraCT numbers cannot be confirmed, a statement should be added to alert NCAs that the information may not be exhaustive.

…../……/…….. *[date]*

Name and signature of the authorised person of the Competent Authority of *[country]*[3]

[Name, title, national authority, phone numbers and e-mail in case of enquiries]

[3] The signature, date and contact details should appear on each page of the non-compliance document.