INSTRUCTION ON THE OBLIGATIONS OF MANUFACTURERS IN ACCORDANCE WITH ARTICLE 100 OF THE LAW ON MEDICINAL PRODUCTS („Official Gazette of Montenegro“, No 14/26)

For the purpose of safeguarding public health and ensuring consistent implementation of the Law on Medicinal Products (“Official Gazette of Montenegro”, No. 14/26), this Instruction provides a more detailed description of the obligations of manufacturers as stipulated in Article 100, paragraphs 1 and 2 of the Law on Medicinal Products.

Article 100, paragraph 2 of the Law on Medicinal Products provide as follows:

The manufacturer shall investigate any deviations in the manufacturing process and notify the Institute without delay of any such deviations, as well as of any other circumstances that may give rise to suspicion regarding quality, safety, and efficacy of the medicinal product.

Examples of situations requiring notification to Institute by the manufacturer without delay are listed below:

1. Placement under a Compliance management programme by regulatory authorities of other countries.
2. Receipt of a Statement of Non-Compliance or suspension/revocation of a GMP certificate issued by regulatory authorities of other countries.
3. Issuance of a Statement of Non-Compliance for an API manufacturer by an EU regulatory authority, or revocation of CEP by the EDQM.
4. Situations leading to disruption of supply to the market and potential shortages (e.g. issues with suppliers of starting materials).
5. Failed simulation of the aseptic process.
6. Failed validation of the sterilisation process.
7. Failure of sterility testing during final product testing.
8. Cases of cross-contamination and mix-ups.
9. Out-of-Specification (OOS) results with potential impact on the market (e.g. OOS results obtained during testing of samples from stability studies).
10. Quality defects identified after batch release to the market (e.g. presence of foreign particles such as glass, metal, fibres, etc., compromised container closure integrity, mislabelling).
11. Fire, flood, interruption of electricity supply, municipal water supply, or other incidents that may impact the manufacturing site.
12. Failures on the manufacturing line resulting in a prolonged interruption of operations.
13. Installation of new equipment leading to a prolonged interruption of operations.
14. Breach of data integrity, e.g. altered or deleted chromatographic data, compromised user account security, backdated records, uncontrolled audit trails, etc.

In the above-mentioned cases, as well as in any other situations that may give rise to suspicion regarding quality, safety, and efficacy of the medicinal product, the manufacturer shall:

- notify the Institute for Medicines and Medical Devices without delay, by email or formal written communication;
- submit an initial report including a risk assessment;
- following completion of the investigation, submit a final investigation report including proposed Corrective and Preventive Actions (CAPA);
- inform the Institute of the status and implementation of CAPA measures.