CInMED
Institute for Medicines and Medical Devices of Montenegro

GUIDELINE FOR REPORTING A SUSPECTED QUALITY DEFECT OF A MEDICINAL PRODUCT

1. Introduction

The Guideline describes the procedure for reporting and documenting deviations from the quality standards of a medicinal product (hereinafter referred to as a *quality defect*), as well as the measures and activities undertaken depending on the classification of the quality defect. The Guideline applies to medicinal products for human and veterinary use (hereinafter: *medicinal product*).

This Guideline covers reports of suspected quality defects of medicinal products, as well as reports of suspected cases of falsified medicines on the market in Montenegro. The Guideline does not apply to medication errors/incidents related to the use of a medicinal product, adverse drug reactions, quality defects or incidents concerning medical devices.

1.1. Reasons for reporting a suspected quality defect of a medicinal product

The most common reasons for reporting a suspected quality defect of a medicinal product include:

- Chemical contamination of the medicinal product;
- Microbiological contamination of the medicinal product;
- Mechanical impurities in the medicinal product (presence of foreign particles);
- Non-compliance with the marketing authorization;
- Out of Trend (OOT) or Out of Specification (OOS) results obtained during stability studies by the manufacturer;
- OOS results obtained during laboratory quality control by an OMCL or another competent regulatory authority of an EU Member State;
- Non-compliance of the manufacture and/or distribution of a medicinal product with the current Guidelines on Good Manufacturing Practice (GMP) and/or Good Distribution Practice (GDP), as determined by the competent inspection, regulatory authorities of EU Member States or by international bodies (e.g., FDA *Warning Letters*, WHO or EDQM *Notices of Concern*);
- Suspension or withdrawal of a Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP);
- Adverse drug reactions (pharmacovigilance) suspected to be related to a quality defect of the medicinal product;
- Suspicion of a falsified medicinal product.

2. Submitting of reports

Notifications of suspected quality defects may be submitted to CInMED by:

- Marketing authorization holders;
- Manufacturers of medicinal products;
- Wholesalers;
- Healthcare professionals;
- Veterinary professionals;
- Sponsors of clinical trials;
- The Ministry of Health, the Veterinary Administration, the Customs Administration, the Ministry of Interior or other state institutions;
- Whistleblowers – usually employees involved in the manufacture of medicinal products or in the manufacturer's quality control laboratories;
- Employees of CInMED.

3. Methods of submitting a report on as suspected quality defect of a medicinal product to CInMED

- In person or by post to the following CInMED address:

  Institut za ljekove i medicinska sredstva
  Bulevar Ivana Crnojevića 64a
  81000 Podgorica
  Crna Gora

- By e-mail to: defekti.kvaliteta@cinmed.me

  For reports submitted via this e-mail address, CInMED is obliged to confirm receipt within 12 hours of receiving the e-mail. If the sender does not receive confirmation of receipt within 12 hours of submission, they should contact CInMED at the following telephone numbers:

  +382 20 310 280 (working days, 07:00–15:00)

  +382 69 512 779 (emergency mobile phone for urgent reports outside working hours, weekends, and public holidays).

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4. Procedures covered by the reporting of a suspected quality defect of a medicinal product

4.1. Reporting of a suspected quality defect by a patient and/or healthcare professional

When a patient suspects a lack of efficacy of a medicinal product, experiences unexpected adverse reactions not described in the Package Leaflet, or notices deficiencies in the quality or packaging of the product, they should contact a pharmacist or physician.

A patient may report a suspected quality defect to the healthcare professional who prescribed the medicine or to the pharmacist who dispensed it. It is important that the patient does not discontinue therapy on their own initiative and that they always consult their physician or pharmacist.

A healthcare professional who detects a quality defect of a medicinal product, or to whom a patient has reported a suspected quality defect, must immediately stop dispensing medicines from the same batch to patients and, without delay, complete the *Reporting Form for Suspected Quality Defects or Deviations from Quality Standards* (Za851.85-IMS) (available on the CInMED portal) and submit the report to CInMED.

A veterinary professional who detects a quality defect of a medicinal product must immediately stop the administration/dispensing of medicines from the same batch and, without delay, complete and submit the report of the suspected quality defect to CInMED.

The batch of the medicinal product for which a suspected quality defect has been identified or reported must be separated from other available batches of the same product and placed under quarantine.

4.1.1. Initial Assessment of a Suspected Quality Defect by a Healthcare/Veterinary Professional

When healthcare or veterinary professionals suspect a quality defect of a medicinal product, or receive a report from a patient, they perform an initial assessment. In this process, healthcare/veterinary professionals may also contact CInMED to request additional information.

The obligations of healthcare/veterinary professionals include:

- Assessing whether the event is an adverse incident caused by a medicinal product that deviates from quality standards, or an adverse drug reaction;
- Assessing whether the event is an adverse incident caused by a medicinal product that deviates from quality standards, or by a medical device used for administration of the medicinal product (and which is not an integral part of the product);
- Collecting the necessary information prior to reporting the suspected quality defect;
- Discontinuing the dispensing of medicines from the same batch for which a quality defect has been reported;
- Retaining samples of the medicinal product for which a suspected quality defect has been reported;
- If there is a suspicion that the adverse event in the patient may be related to a suspected quality defect, the healthcare/veterinary professional should verify:
    - whether the product was stored correctly (to exclude improper storage as the cause of the quality defect);
    - if the quality defect is visible, whether it was identified in a new unopened package or in a package that had already been used (to exclude user errors such as product mix-ups);
    - whether other unopened packages of the same batch are available for verification;
    - if the product requires prior preparation (e.g. reconstitution with a solvent), whether the procedure was performed correctly and/or whether the correct solvent was used;
    - whether the medicinal product was used in accordance with the physician’s and pharmacist’s instructions and the Package Leaflet;
    - if the medicinal product was used with a medical device, whether the device could have caused the adverse event.

A careful assessment of the case must be conducted to determine whether a suspicion of a quality defect exists. If such suspicion is established, it must be reported.

Even in cases where not all data are available, the suspected quality defect must be reported without delay, and the missing information should be provided subsequently.

4.2. Reporting of a Suspected Quality Defect by the Marketing Authorization Holder, Manufacturer, Wholesaler, and Clinical Trial Sponsor

It is the obligation of the marketing authorization holder, the manufacturer, wholesalers, and clinical trial sponsors to promptly inform CInMED whenever they become aware of a suspected or confirmed quality defect of a medicinal product.

In the event of a suspected or established quality defect, the marketing authorization holder, the manufacturer, wholesalers, and clinical trial sponsors are required to:

- ensure an effective system for recording and investigating the root causes of the quality defect;
- submit a detailed report and supporting data to CInMED, thereby enabling appropriate conclusions to be drawn.

5. Data and documentation to be submitted to CInMED

When submitting a report of a suspected quality defect, the *Reporting Form for Suspected Quality Defects or Deviations from Quality Standards* (Za851.85-IMS), available on the CInMED portal, must be completed. In addition to the completed Form, supporting documentation must also be submitted to CInMED, where applicable.

The reporter should include at least the following information in the above-mentioned Form:

- details of the medicinal product and the batch(es) concerned;
- a detailed description of the identified deviation from quality standards;
- an assessment of the classification of the deviation from quality standards;
- a history of the incident (when it occurred and/or when it was observed);
- the possible root cause of the deviation;
- a description of corrective and preventive actions (CAPA);
- activities undertaken by regulatory authorities of other countries where the medicinal product is on the market;
- distribution data of the affected batch(es);
- a proposal for the level of product recall, if applicable;
- conclusion.

CInMED may request the marketing authorization holder or manufacturer to carry out an investigation into the quality defect (Investigation Report). The investigation may include:

- review of manufacturing and analytical documentation and equipment logs to determine the root cause of the defect;
- review of all related manufacturing, packaging, testing, and batch release records, as well as irregularities during distribution that may explain the suspected deviation from quality standards;
- analysis of retention samples;
- review of similar deviations or complaints recorded for the same or other batches;
- assessment of the impact of the defect on the efficacy and safety of the medicinal product;
- risk assessment by the marketing authorization holder, including a medical risk assessment, if necessary;
- description of CAPA to be implemented by the marketing authorization holder to prevent recurrence of such quality defects in the future;
- determination of the quantity of the medicinal product affected by the defect.

The marketing authorization holder must provide CInMED in writing with information on all actions taken and the implementation of risk management measures defined during the quality defect assessment process.

5.1. Classes of Quality Defects of Medicinal Products

When reporting a suspected quality defect of a medicinal product in the *Reporting Form for Suspected Quality Defects or Deviations from Quality Standards* (Za851.85-IMS), the estimated defect classification must be indicated. Following verification, CInMED either approves the proposed classification of the reported quality defect or, if the incorrect class has been indicated, informs the reporter thereof by e-mail.

Depending on the level of risk for the patient/user, a quality defect may be classified as follows:

1. **Class I** – defects potentially life-threatening or with serious health consequences, such as:
- Wrong medicinal product (labelling and contents do not correspond to the same medicine);
- Correct medicine but wrong strength, which may result in serious medical consequences;
- Microbiological contamination in sterile injectable or ophthalmic medicinal products;
- Chemical contamination that may lead to serious medical consequences;
- Product mix-up involving more than one package;
- Wrong active substance in a product containing multiple active substances, with serious medical consequences.

2. **Class II** – defects that may cause illness or incorrect treatment but are not life-threatening and do not fall under Class I, such as:
- Incorrect labelling, e.g. wrong or missing text/picture on the packaging of the medicinal product;
- Absence of the Package Leaflet or incorrect information in the Package Leaflet;
- Microbiological contamination of sterile products other than sterile injectables or ophthalmic products, with possible medical consequences;
- Chemical or physical contamination (excessive level of impurities, contamination with other medicines – cross-contamination, particles);
- Non-compliance with specifications (content/stability, fill/weight for single-dose containers, related substances);
- Unsafe closure with serious medical consequences (e.g. cytotoxic medicines, potent medicines, containers with child-resistant features).

3. **Class III** – defects unlikely to cause serious health consequences but which may lead to suspension of placing the product on the market or its recall for other reasons, such as:
- Packaging errors, e.g. wrong or missing batch number or expiry date;
- Improper closure (non-sterile medicinal products);
- Microbiological, physical, or chemical contamination unlikely to have medical consequences.

6. Activities that may be undertaken following the evaluation of a reported quality defect of a medicinal product

After receiving a report of a suspected quality defect of a medicinal product, CInMED evaluates the submitted information, performs a risk assessment, and decides on one or more of the following actions:

- Temporary suspension of placing the medicinal product/batch on the market (quarantine of the remaining quantities), applied as a preventive and interim measure in cases where there is insufficient information to make a final risk assessment and decision;
- Recall of the medicinal product/batch from the market;
- Temporary interruption or permanent discontinuation of a clinical trial;
- Restriction of use of the medicinal product;
- Permanent suspension of placing the medicinal product/batch on the market (cessation of further supply of the affected batches);
- Extraordinary GMP/GDP inspection;
- Repackaging of the product or correction of labelling to eliminate the defect;
- Distribution of notifications/letters to healthcare or veterinary professionals;
- Publication of quality defect notices on the CInMED website;
- Investigation by the marketing authorization holder or manufacturer and implementation of corrective and preventive actions (CAPA);
- Extraordinary quality control testing of the affected product;

- Monitoring of ongoing stability studies;
- Archiving without taking further action;
- Other measures deemed necessary (e.g. extraordinary inspection, variation of the marketing authorization, or other regulatory measures).

If CInMED decides that recall of the medicinal product/batch from the market is necessary, the recall must be initiated within the following timelines, depending on the classification of the quality defect:

- within 24 hours for Class I;
- within 48 hours for Class II;
- within 5 days for Class III.

7. Terms and definitions

Falsified medicinal product – a medicinal product that is deliberately and fraudulently misrepresented with respect to:

- its **identity**, including packaging and labelling, name, or composition regarding any ingredient of the product, including excipients and strength;
- its **origin**, including the manufacturer, the country of manufacture, the country of origin, or the marketing authorization holder;
- its **traceability**, including records and documents relating to the distribution of the medicinal product.

This definition does not apply to medicines with unintentional quality defects and does not cover issues related to intellectual property rights infringement.

Incident – an unforeseen event, accident, or error in the manufacture or distribution of a medicinal product, or other situations giving rise to suspicion about the quality, efficacy, or safety of the medicinal product.

Quality of a medicinal product – the property of a medicinal product that can be established by quality testing of all its components and represents acceptable physical, chemical, biological, pharmaceutical-technological, and other characteristics of the product, in accordance with the requirements set out in the marketing authorization.

Suspected defective medicinal product – a medicinal product for which a report of suspected quality defect has been submitted, indicating that the quality of the product is inadequate or that it does not comply with the quality defined in the marketing authorization.

Adverse event – any untoward medical occurrence during treatment with a medicinal product, for which a causal relationship with the product does not necessarily have to be proven; it represents any unintended and undesirable sign (e.g. abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product.

Adverse drug reaction – a harmful and unintended response to a medicinal product.

Suspension of marketing / batch release – an administrative ban imposed by the Institute, lasting until the completion of quality verification or benefit–risk assessment of the medicinal product. The suspension may result either in the reinstatement of the product on the market or in its recall.

Batch recall – the action of withdrawing a batch of a medicinal product from the distribution chain and from users. A recall may be partial, when the batch is withdrawn only from certain wholesalers and/or users, or complete, when the batch is withdrawn from the entire Montenegrin market.

Sponsor of a clinical trial – a natural or legal person responsible for initiating, conducting, and/or financing a clinical trial.

Substandard medicinal products – medicinal products manufactured in a way that does not meet established quality standards or specification requirements, or both.

8. Abbreviations

CAPA (Corrective and Preventive Actions) – corrective and preventive measures
CEP (Certificate of Suitability) – Certificate of Suitability to the Monographs of the Ph. Eur.
FDA (U.S. Food and Drug Administration) – United States Food and Drug Administration
EDQM & HealthCare (European Directorate for the Quality of Medicines & HealthCare) – European Directorate for the Quality of Medicines & HealthCare
OMCL (Official Medicines Control Laboratory) – laboratory performing quality control testing of medicinal products on behalf of the regulatory authority, independent of the manufacturer and the marketing authorization holder
OOS (Out of Specification) – results falling outside the specification limits approved in the marketing authorization, renewal, or variation procedure
OOT (Out of Trend) – a result that does not follow the expected trend when compared with other results from previous laboratory tests performed using the same method. An OOT result is not necessarily an OOS.
WHO (World Health Organization) – World Health Organization