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Management and classification of reports of suspected quality defects in medicinal products and risk-based decision-making

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1. Scope

The scope of this procedure relates to the managing by EU competent authorities of reports of suspected quality defects identified in medicinal products or active pharmaceutical ingredients (API) for humans and animals.

This procedure provides detailed guidance on risk assessment methodology that can be utilised by National Competent Authorities (NCAs) in order to reach regulatory risk mitigating decisions especially in the context of Member States considering the issue of a Rapid Alert notification.

2. Introduction

2.1 Harmonisation of procedures utilised in defect assessment and further categorisation and rapid alert transmission is essential to:

- quickly identify the level of impact of the defect on patients/end users,
- reach a common harmonised decision among Competent Authorities,
- promote mutual reliance between Member States and partner authorities.

Revision and update of procedures are also beneficial in keeping the knowledge up to date.

2.2 Holders of an authorisation, such as manufacturers and importers of medicinal products, (as per Article 40 of Directive 2001/83/EC and Article 88 of Regulation 2019/6) are obliged to report to the concerned Competent Authorities any defect in a medicinal product within the scope of their authorisation that could result in a recall or abnormal restriction in supply (as per Article 13 of Directive (EU) / 2017/1572, or Article 13 of Directive 91/412/EEC and EU Good Manufacturing Practice guides). This includes possibly faulty manufacture, product deterioration, detection of falsified medicines or any other serious quality problems with a product. In the event of a serious or potentially life-threatening situation identified for API used as starting materials, the local, national, and/or international authorities should be also informed, and their advice sought.

2.3 Reports of suspected defects may also be sent to the authorities by other competent authorities, health professionals, wholesale dealers and members of the general public the local, national, and/or international authorities. These reports might include quality defects on APIs used as starting materials and in addition, also adverse drug reactions due to a defect in the quality of the product concerned.

Official Medicines Control Laboratories may also report to their competent authorities confirmed out of specification results from testing medicinal products on the market requiring further risk assessment.

2.4 Member States are obliged to take all appropriate measures to ensure that a medicinal product is withdrawn from the market if it proves to be harmful under normal conditions of use, if its composition is not as declared or if the controls on the finished product or during the manufacturing process or other requirement of the manufacturing authorisation has not been fulfilled (Article 117 of Directive 2001/83/EC and Article 134 of Regulation 2019/6).

2.5 Each Competent Authority should have a written procedure that covers the receipt, the managing and the risk assessment of notifications of suspected defective products and batch recalls from companies or health professionals during and outside normal working hours.

2.6 Each competent authority should have a team of defined qualified experts capable to perform the initial professional risk-based assessment of the quality defect in accordance with the risk posed by the quality issue.

2.7 It is the responsibility of the company to undertake the actions recommended by the competent authority, including market actions where warranted.

2.8 In case of an agreed batch recall, it is normally the responsibility of the company to recall a batch and to notify concerned authorities, professionals of the distribution chain and customers in accordance with EU Good Manufacturing Practice guides.

2.9 It is responsibility of the Competent Authority of the Member State in which the recall occurred to notify other authorities about the recall. Responsibilities for notifying health professionals, media and the general public may vary between Member States.

2.10 It is responsibility of the competent authority to oversee the company's necessary investigation to identify the route cause(s) of the quality defect.

2.11 The present procedure should be read in conjunction with "Procedure for managing rapid alert arising from quality defect risk assessment should be used to reach a risk-based classification" and its related Appendix I "Guidance in relation to the risk-based classification and decision-making for quality defects, recalls, rapid alerts and risk reviews".

3. Definitions

3.1 **Recall action**. The action of retrieving one or more batch (es) from the distribution chain and users. A batch recall may be partial, in that the batch is only recalled from selected distributors or users. The extent of the recall of a batch is defined by quality risk associated and can go from a recall on patients level (including owners of animals) to a recall limited to community pharmacies, veterinarians or wholesalers.. Batch recalls may or may not be accompanied by withdrawal of a marketing authorisation.

3.2 **Quality defect report.** A report, usually a standard template in use by the receiving authority, informing about a quality defect issue impacting one of more batch (es) of a certain medicinal product or API for human or veterinary use.

3.3 **Rapid Alert for Quality Defects/Recall action**. Notification of urgent information on quality defects from one competent authority to other authorities. The information transmitted can be related to a batch recall action that has been instituted in the country originating the rapid alert and may concern other authorities. A rapid alert may also concern a quality defect or other serious information, regardless of whether a recall action has been initiated in the originating country.

3.4 **Risk based classification**. Classification of a quality defect based on the risk posed by the issue on public and animal health.

3.5 **Risk based decision.** A decision made taking into consideration the risk posed by a quality defect on public and animal health and aiming at mitigating or preventing the impact.

3.6 **Suspected defective product**. A medicinal product about which a report has been received suggesting that it is not of the correct quality, as defined by its Marketing Authorisation.

4. Management and assessment process

4.1 Aim

4.1.1 To record, assess and classify, during and outside office hours, reports of suspected defective products and to assess and oversee appropriate corrective and preventive actions (CAPAs) with appropriate urgency.

4.2 Receiving quality defect report

4.2.1 Contact details for reporting suspected defective medicinal products to the Competent Authority should be made widely known and readily available to those likely to need to make a report. This would include manufacturers and marketing authorisation holders and may also include wholesalers, hospitals, pharmacists, veterinary practitioners and local health authorities.

A dedicated, continuously manned telephone line is preferred. Arrangements should be made to divert calls if necessary during out-of-office hours. If other means such as e-mail or fax are used they should be monitored frequently, including during out-of-office hours.

4.2.2 Every contact should be recorded, using a standard format for recording information. A file should be created for each suspected defect in order to collect information as it becomes available. All correspondence related to the specific defect should contain in the e-mail subject line key information that facilitate immediate understanding (e.g. indication on whether the product is for human (H) or veterinary (V) use or for or (H/V). (e.g. quality defect identification number/V/product name/…).

4.2.3 The Competent Authority assessing the defect should make sure to obtain direct personal contacts of the main parties involved, especially the person making the report, the person coordinating action for the company (usually the Qualified Person (QP)), and, case by case, the inspector familiar with the manufacturer or importer and persons responsible for vigilance within the Competent Authority.

All relevant information obtained verbally should be confirmed in writing.

4.2.4 The report should be referred with minimum delay to a person(s) in charge of the initial professional risk-based assessment of the quality defect. A target time should be set for reports to be referred to this person, normally during the working day. It may be possible to give guidance to the person receiving out-of-hours reports on the nature of reports which must be relayed to the professional assessor before the next routine working day.

4.3 Assigning a risk-based classification to the defect

4.3.1 A formal risk-based classification of the defect should be performed in a timely manner. The guidance contained in Part I of Appendix 1 of "Procedure for managing rapid alert arising from quality defect risk assessment should be used to reach a risk-based classification".

Three levels of risk may be assigned to quality defect issues:

1. High Risk
2. Moderate Risk
3. Low Risk

4.3.2 Some cases can be qualified as "non-justified" as explained in Part I of Appendix 1 of the Procedure for managing rapid alert arising from quality defect risk assessment.

If the initial professional risk assessment of the report concludes that the defect may represent a high risk issue that could warrant immediate action(s) to protect patient or animal health, the necessary urgent public health safeguarding measures should be

taken without waiting for the creation of the file on the defect issue referred to in step 4.2.2 to be fully in place.

4.3.3 A formal risk-based classification should be assigned to all reports of quality defects.

4.3.4 In order to promote harmonization, the quality defect should also be classified using common standardised terminology.

4.4 Risk-based decision-making

4.4.1 Once a risk-based decision is made on the defect reported, after the defect is classified in one of the four levels of risk above, different types of risk control actions may be agreed. Such actions should be commensurate with the level of risk and should also take into account of potential out of stock situation and clinical issues. Part II of Appendix 1 of the Procedure for managing rapid alert arising from quality defect risk assessment.

This may involve one or more of the following actions, according to the national procedures:

- Filing without follow-up (no further action required)
- Product quarantine action (e.g. at wholesale level) - this is a precautionary and interim measure useful where insufficient information is available to make immediately a final risk-based assessment and decision. Prevents further defective units being distributed, pending the availability of sufficient information to facilitate a final decision concerning market action.
- Batch or product recalls.
- Interruption / cessation of a clinical trial.
- Cessation of certification and release of any new defective batches.
- Cessation of supply of additional units of affected batches.
- Inspection of packs for the defect (e.g. at wholesalers) - to remove those that are defective.
- Reworking of packs to remove the defect.
- Caution-in-Use Notification (CIUN) / Dear Healthcare Professional Communication (DHPC).
- Communications / statements to the general public.
- Monitoring on-going stability study.
- Assessment of other batches of the same product or other products that could be affected by the same quality defect.

Note: in some cases, especially for low risk quality defects, none of the above actions may be warranted. It may be sufficient to direct the company to focus on the root causes of the defect and to ensure that effective corrective and preventative actions (CAPAs) are implemented for it and that the authorities are duly informed of the effectiveness of the implementation.

4.5 Samples

4.5.1 Wherever possible and when considered useful, samples of the product(s) involved in the defect report should be obtained by the Competent Authority. The samples should be analysed by an Official Medicines Control Laboratory as agreed by the Competent Authority. In certain cases samples should be provided to the company for analysis

under full supervision of the Competent Authority. Results should always be made available to all interested parties.

4.6 Inspection

4.6.1 If necessary, the inspector usually associated with the manufacturing or importing site is made aware of the report, and comments on general GMP compliance and on the related products.

4.6.2 When necessary an on-site inspection is performed to assess notably batch records of the product concerned, plant records and records of other batches or products which could also be affected.

4.6.3 Samples of the batch concerned, related batches and related starting materials may be taken and analysed. This could also be applied to inspections coordinated by and conducted on behalf of the European Medicines Agency.

4.7 Documenting and communicating the risk-based decision

Having considered all the available information, including the need to make a decision without waiting for full information to be available because of the potential risk to public health, the decision, based on the risk assessment of the defect as per the guidance in Part 2 of Appendix 1, should be formally documented and communicated as appropriate.

NCAs are encouraged to discuss and communicate quality defects issues among themselves as well as their risk-based decisions with other NCAs through the rapid alert network, where needed.

The exact wording of any notification (such as a product recall or a DHPC) should be checked and, if possible, agreed with the company. Particular attention should be paid to the correctness of the batch number(s), expiry dates, product names in the different countries, pharmaceutical form, strength and relevant medicinal product code (e.g. marketing authorisation number). Advice should be given on where further information may be obtained (normally from the company).

The distribution of the notification to interested parties within the authorities should be agreed. This may include national Ministers and other government departments, government press officers and, by means of a Rapid Alert, authorities and organisations in other countries (EEA, MRA Partners, PIC/S participating authorities, WHO, others).

As far as possible standard formats, wording and distribution lists should be used for the notifications with the aim of ease of understanding by the recipient and lack of ambiguity.

4.8 Validating the Risk-based Decision

4.8.1 According to the national Competent Authority procedures, approval should be obtained for the proposed action by the relevant quality defect team or other staff within the Competent Authority.

4.9 Implementing the risk-based Decision

4.9.1 Refer to "Procedure for managing rapid alerts arising from quality defects risk assessment" and/or the corresponding national procedure.

4.10 Follow-up

4.10.1 There should be consideration of what, if any, action to take concerning the Marketing or Manufacturing Authorisations and their holders. This includes the evaluation of a possible for cause inspection, where required.

4.10.2 The Inspectorate/ quality defect assessment unit should assess the follow-up actions by the company, including the reconciliation of issued, returned and remaining stocks, the investigation into the cause of the defect and actions to prevent a repetition.

4.10.3 Completion of any follow-up actions should be checked. This can include, for example, completing and organising records and archiving according to national procedures.

4.10.4 At national level risk review of selected quality defect investigations should be conducted. Such risk review should be performed on a voluntary basis by competent authorities, with a view to determine whether the key risks presented by the defective medicinal product were actually identified and managed effectively. Part IV of Appendix 1 provides guidance in this regard.

5. Quality assurance

5.1 All procedures should be documented and maintained up to date.

5.2 Contact lists for officials and companies should be maintained up-to-date and should be verified at intervals (e.g. a rolling programme of annual checks of company contacts, possibly as part of GMP inspections).

5.3 All staff who could be involved in receiving a report of a suspected defective product, in the risk-based decision-making process or in managing a Rapid Alert, should be trained in the relevant procedures and have access to a copy of the Standard Operating Procedures (SOPs) and report forms wherever they may be required to act (including at home if they are on call outside-office hour.