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HANDLING OF REPORTS OF SUSPECTED QUALITY DEFECTS IN MEDICINAL PRODUCTS

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HANDLING OF REPORTS OF SUSPECTED QUALITY DEFECTS IN MEDICINAL PRODUCTS

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HANDLING OF REPORTS OF SUSPECTED QUALITY DEFECTS IN MEDICINAL PRODUCTS

1. Scope

This guidance covers the handling of reports of suspected quality defects in medicinal products for humans and animals made to a Competent Authority before, if necessary, a Rapid Alert is transmitted. It recommends the elements of a procedure for receiving, assessing and categorising reports of suspected defective products that necessarily precedes a Rapid Alert.

2. Introduction

2.1. Discussion at the Inspectors' WP and elsewhere has indicated the need to harmonise the handling of reports of suspected quality defects in medicinal products and confirm mutual confidence in member states' procedures for assessing the need to transmit a Rapid Alert of a quality defect.

2.2. Holders of an authorisation under Article 40 of Directive 2001/83/EC and under Article 44 of Directive 2001/82/EC (i.e. manufacturers and importers of medicinal products) are obliged under Article 13 of Directive 91/356/EEC and Article 13 of Directive 91/412/EEC and GMP Guide 8.8 to report to their Competent Authority any defect in a medicinal product handled under their authorisation that could result in a recall or abnormal restriction in supply. It is normally the Qualified Person who has this responsibility.

Reports of suspected defects may also be sent to the authorities by health professionals, wholesale dealers and members of the general public. In addition, a report of an adverse drug reaction may in fact be due to a defect in the quality of the product concerned.

2.3. Member States are obliged to take all appropriate measures to ensure that a medicinal products is withdrawn from the market if it proves to be harmful under normal conditions of use, if its composition is not as declared or if the controls on the finished product or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 83 of Directive 2001/82/EC].

2.4. It is normally the responsibility of the company to recall a batch and to notify customers accordingly. It is normally the responsibility of the Competent Authority to notify other authorities of the recall. Responsibilities for notifying health professionals, media and the general public may vary between member states.

3. Definitions

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.
Batch recall. The action of withdrawing a batch from the distribution chain and users. A batch recall may be partial, in that the batch is only withdrawn from selected distributors or users.
Rapid Alert. An urgent notification from one competent authority to other authorities that a batch recall has been instituted in the country originating the rapid alert. The procedure for issuing rapid alerts is defined in the Compilation of Community Procedures, May 2001[1].

4. Handling Process

4.1 Aim

To record and assess, during and outside office hours, reports of suspected defective products and to implement action with appropriate urgency.

4.2 Process Steps

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 MA 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 fax or e-mail 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. The first informant is unlikely to have all the required information so it is most important that a contact is agreed from whom further information may be obtained. A registered file should be established for each suspected defect to collect information as it becomes available.

4.2.3. The report should be referred with minimum delay to a person(s) able to make an initial professional assessment of the nature, extent and urgency of possible public health risk. A target time should be set for reports to be referred to this person, normally less than one hour. 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.

4.2.4. The initial professional assessment should include the following considerations:
- risk to health of an individual (human or animal) if the suspected defect is real (consider risk to vulnerable patients as well as normal individuals, risk of not receiving the correct medication, risk from incorrect dosage (consider the therapeutic index), long-term risk as well as immediate risk (e.g. if a complete dispensed container is faulty the impact on the individual will be cumulative, risk to persons administrating a defective veterinary medicinal product, risk to the consumer of animal foodstuff in view of possible residues in the foodstuff):
- probability that the defect is real and occurs in the medicine supplied by the manufacturer (e.g. not a clinical effect with a different cause, not a defect introduced at the time of dispensing).
- in the case of suspicion of defective vaccines (cross contamination with a virus), risk of distorting the analysis in national programmes against certain viral diseases.

4.2.5. At this stage it will be decided whether the potential hazard to health is such that extraordinary measures must be taken (including the convening of an emergency action group out-of-office hours) or whether further consideration may be left for normal office hours.

4.2.6. Further professional assessment of the risk from the product should involve discussion with the manufacturer and include consideration of:
- any other reports which may be related;
- the distribution of the batch (e.g. restricted to known hospitals, widespread through wholesalers);
- date of first distribution and last distribution;

- any remaining stock with the manufacturer;
- probability that other batches are affected in the same way, and their distribution.

4.2.7. If a recall is being considered extremely important issues to consider include:
- possibility of an out-of stock situation;
- availability of alternative products;
- clinical effect of a disruption in supply.

Note: No supply of a product may be worse than use of product with a suspected deficiency.

4.2.8. Direct personal contacts are important, especially with the person making the report, the person co-ordinating action for the company (usually the QP), the inspector familiar with the manufacturer and persons responsible for vigilance within the Competent Authority.

It is often helpful in detailed discussions if communications are between professional equivalents, e.g. medical assessor with medical staff of the company, inspectors with QPs or production staff, analytical assessors with QC staff, etc.

All information obtained verbally should be confirmed in writing.

4.3 Samples

Wherever possible the sample involved in the defect report should be obtained by the Competent Authority. It should normally be examined by an Official Medicines Control Laboratory as agreed by the Competent Authority. In certain cases samples should be provided to the company for examination under full supervision of the Competent Authority. Results should always be made available to the company.

Note*: A company should have instructions for release of retained samples in order not to have all of them used up during an emergency situation other than with consent from the Competent Authority.*

4.4 Inspection

The inspector normally associated with the manufacturing site should be made aware of the report and may comment on general GMP compliance and what related products made.

On-site inspection may be required to assess batch records of the product concerned, plant records and records of other batches or products which could also be affected.

Samples may be taken of the batch concerned, related batches and related starting materials. When considering taking material from the company's retained samples, consideration must be given to the quantity available and all tests which may be required for further investigations. These may be prescribed by the MA and/or national requirements. This could also be applied to the European Agency.

4.5 Preparing a Decision

4.5.1. 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, a decision will be taken on appropriate action, which may be one or more of the following according to national procedures:
- filing without follow-up (no further action);
- further investigation;
- quarantine of remaining stock at manufacturer and quarantine or recall at wholesalers either While further investigation occurs or to prevent further distribution even if a full recall is not required;
- GMP measures to avoid a recurrence;
- distribution of a 'caution in use' notice to concerned health professionals;

- notification of the batch recall to selected health professionals (e.g. particular hospitals, clinics, dentists);
- notification of the batch recall to all health professionals (e.g. including all hospitals, doctors, community pharmacies, veterinary practitioners etc.);
- notification of the batch recall through the media;
- publication on the competent authority website, newsletter or similar.
- an assessment should be made if other batches of the same products or other products could be affected the same GMP deficiency.

The exact wording of any notification should be checked and if possible agreed with the company. Particular attention should be paid to check the batch number(s), expiry dates and product name and strength. 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[1], authorities and organisations in other countries (EU/EEA, MRA Partners, PIC/S, 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.

4.6 Validating the Decision
According to the national Competent Authority procedures, approval should be obtained for the proposed action.

4.7 Implementing the Decision
Refer to national procedures and the EU Rapid Alert Procedure[1].

4.8 Follow-Up

4.8.1. There should be consideration of what if any action to take concerning the Marketing or Manufacturing Authorisations and their holders.

4.8.2. The Inspectorate should asses 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.

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

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 or handling a Rapid Alert should be trained in the relevant procedures and have access to a copy of the SOPs and report forms wherever they may be required to act (including at home if they are on call outside-office hours).

5.4. It is particularly important that those procedures which may need to be followed by staff not routinely involved (e.g. called upon as a reserve) and/or required to be involved when away from their office should be detailed and easy to follow.

Reference.

1. ‘Compilation of Community Procedures on Inspections and Exchange of Information ’ October 2003.