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PROCEDURE FOR HANDLING RAPID ALERTS AND RECALLS ARISING FROM QUALITY DEFECTS

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PROCEDURE FOR HANDLING RAPID ALERTS AND RECALLS ARISING FROM QUALITY DEFECTS

Guideline Title:	Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects
Adopted:	7 July 2004 minor modification agreed September 2005.
Date of entry into force:	1 September 2004. (The minor modification is immediately applicable following agreement)
Supersedes:	Version in force from 28 July 2003.
Reason for Revision:	Minor amendment to section 4.1.2, as a result of experience gained, introducing some flexibility on which Competent Authority should take responsibilty for issuing a rapid alert.
Notes:	Pharmacovigilance alerts are not included within the scope of this procedure. For information on procedures for pharmacovigilance rapid alerts, reference should be made to document reference CPMP/PhVWP/005/96, rev. 1 *Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in human pharmacovigilance* or subsequent updates.

Content:

PROCEDUR E FOR HANDLING RAPID ALERTS AND RECALLS ARISING FROM QUALITY DEFECTS

1. Scope

This procedure covers the transmission of information by means of a rapid alert between the Competent Authorities of EU and EEA countries (the "Member States"), CADREAC, PIC/S, EDQM and MRA partners relating to the recall of medicinal products which have quality defects, including counterfeit or tampered products, when urgent action is required to protect public health and animal health. The procedure may be used also for transmission of other information such as cautions-in-use, product withdrawals for safety reasons or for follow-up messages to any of the above listed categories. This procedure covers both human and veterinary medicinal products and operates within the scope of the relevant Two Way Alert programmes established between Member States and MRA partners. Pharmacovigilance or Medical Device alerts are not included within the scope of this procedure.

2. Introduction

2.1. In order to protect public health and animal health, it may become necessary to implement urgent measures such as the recall of one or more defective batch (es) of a medicinal product during its marketing period.

2.2. Each holder of an authorisation referred to in Article 40 of Directive 2001/83/EEC or Article 44 of Directive 2001/82/EC (for veterinary products) is required by Article 13 of Directive 2003/94/EC or Article 13 of Directive 91/412/EEC (for veterinary products) to implement an effective procedure for the recall of defective products. The authorisation holder is required to notify the relevant Competent Authority of any defect that could result in a recall and indicate, as far as possible, the countries of destination of the defective product.

2.3. In addition, for centrally authorised products Council Regulation (EEC) 2309/93, Art. 15(2) or Article 37(2) of Regulation 2309/93 (for veterinary products) the MAH is obliged to keep the EMEA informed of certain new information (e.g. suspension of the manufacturing authorisation, FDA Warning Letters, etc)

2.4. Each Competent Authority should have a written procedure that covers the receipt and handling of notifications of suspected defective products and batch recalls from companies or health professionals both during and outside normal working hours.

2.5. The Competent Authority of each Member State should assist the authorisation holder in the recall process, as appropriate, and monitor its effectiveness. The Competent Authority should ensure that information concerning the recall of medicinal products is notified rapidly to other Member States, if the nature of the defect presents a serious risk to public health. This information should be transmitted by means of the "Rapid Alert System".

2.6. Each Competent Authority should have a written procedure that covers the issue of rapid alerts both during and outside normal working hours (if the urgency of the situation warrants such action).

3. Criteria for Issuing a Rapid Alert

3.1. The aim of the Rapid Alert System is to transmit only those alerts whose urgency and seriousness cannot permit any delay in transmission. To ensure its effectiveness, the system must not be saturated by the transmission of less urgent information. In each case a professional assessment must be made of the seriousness of the defect, its potential for causing harm to the patient or (in the case of a veterinary product) harm to animals, consumers, operators and the environment, and the likely distribution of the affected batch(es). Appendix 1 provides guidance on the classification of the urgency of the recall of defective medicinal products.

3.2. Class I defects are potentially life threatening. A rapid alert notification must be sent to all Member States, CADREAC countries, PIC/S, EDQM and MRA partners, irrespective of whether or not the batch was exported to that country.

3.3. Class II defects could cause illness or mistreatment, but are not Class I. A rapid alert notification should be sent only to those Member States, CADREAC countries, PIC/S, EDQM and MRA partners to which it is known, or believed, that the batch has been distributed. In identifying those countries, due consideration should be given to parallel distribution and import arrangements and the free trade between wholesale distributors within the EEA. In the case of parallel imports where there is difficulty in establishing the traceability of batches, consideration should be given to notifying all Member States through the Rapid Alert System.

3.4. Class III defects may not pose a significant hazard to health, but withdrawal may be initiated for other reasons. These are not notified through the Rapid Alert System.

3.5. Where appropriate, the rapid alert system may be used for notification to Member States or MRA partners of the recall of products or an embargo on the distribution of products following suspension or withdrawal of a manufacturing authorisation.

4. Issue of a Rapid Alert Notification

Responsibility

4.1. For a batch manufactured in a Member State, or a batch manufactured in a third country and imported into the EEA, which is the subject of a national or mutually recognised (decentralised) marketing authorisation, the Competent Authority of the Member State in which the defect was first identified should investigate the defect and issue the rapid alert. MRA partners identified by the manufacturer or importer as countries to which the defective batch was distributed should also be notified through the rapid alert system.

4.2. In the case of a centrally authorised product, and in the exceptional case of a product that has both a centralised and a national authorisation, the Competent Authority of the Member State in which the defect was first identified should lead the investigation of the defect and issue a rapid alert (the issuing authority). The alert should include a recommendation on proposed action for all affected authorities.

When time allows, the issuing authority should, as part of the investigation, come to an agreement on the content of the proposed action with the supervisory authority, the EMEA and the CxMP rapporteur. In some circumstances and especially when the Supervisory Authority has conducted all the investigations, the Member State in which the defect was first identified may delegate to the Supervisory Authority the issuing of the Rapid Alert.

When, due to the urgency of the defect there is not sufficient time to develop a harmonized proposed action this section of the Rapid alert notification should inform all recipients that EMEA will co-ordinate further action in co-operation with the relevant Supervisory Authority, in accordance with EMEA's Crisis Management Procedures and that harmonised follow-up actions will be transmitted through the rapid alert channel when ready

4.3. In the case of parallel distribution of a centrally authorised product and where no repackaging is carried out, the procedure described under 4.2 applies. This procedure also applies if the defect resulted from a repackaging operation. Where repackaging is carried out but the defect results from the original manufacturing process, the procedure described under 4.2 still applies, but the rapid alert should include descriptions of the different packaging in which the product might appear (for example different language versions and pack sizes) where this information is available from EMEA.

4.4. In the case of a parallel import, the Competent Authority of the Member State in which the defect was first identified should issue the rapid alert, notifying MRA partners as appropriate. The Competent Authority should also notify the Supervisory Authority of the Member State in which the batch was manufactured or repackaged depending on the nature of the defect.

Format of the rapid alert and its transmission

4.5. A suitable format for the notification of quality defects by the Rapid Alert System is given in Appendix 2. The form should be completed clearly and (preferably) in English. It should be attached to a distribution list and the documents sent by fax or electronic mail where relevant, to the persons nominated in the EMEA rapid alert list, which includes working hours and out-of-hours contact names and numbers. Changes to contact names and/or numbers must be notified to EMEA so that the list can be updated as necessary.

The rapid alert should be given a reference number with the following format: Country code (country where the original alert was issued)/Region or Authority code (where applicable)/classification/sequential number/correspondence number. (For example ES//II/05/02 would indicate a class II rapid alert initiated by Spain, being the 5th rapid alert initiated by Spain and that it is the second correspondence regarding this rapid alert.)
In the case of a Class I defect which must be notified out of hours, it may be necessary to use the out-of-hours contact telephone numbers in addition to the rapid alert fax.

4.6. Transmission of a Class I rapid alert must be concurrent with the national action. Whenever feasible, transmission of a Class II rapid alert should be concurrent with the national action but in all cases should be within 24 hours of the national notification.

When an authority issues a further rapid alert for a batch, the field 18 in the form in Appendix 2 “Detail of Defect/Reason for recall” should begin with the text: “Rapid Alert following original rapid alert #ref.no.#”.

Action on receiving a notification under the Rapid Alert System:

4.7. Each Competent Authority should have a written procedure for the receipt and handling of rapid alerts from other authorities during and outside working hours. Unless it can be established unequivocally that the defective batch in question has not been distributed in the Member State (including parallel imports) the Competent Authority should apply its national procedure for ensuring recipients of the batch are alerted. The class and urgency of the alert should correspond to those of the initial rapid alert.

5. Fraud and Counterfeit Products

The Rapid Alert System should be used to notify EEA Member States and MRA partners of the possible presence in the distribution network of counterfeit products or those resulting from fraud in manufacture, packaging, distribution or promotion and products containing counterfeit starting materials.

The Competent Authority of the Member State or MRA partner in which the fraud or counterfeit was first detected should issue the notification. The format for a rapid alert notification may be used, but the heading on the document should make clear that the notification relates to fraud or to a counterfeit product and sufficient information should be provided under “details of defect” to enable it to be identified. Notification should be sent to the parties as indicated in section 3.2 for a class 1 defect and concurrently to EMEA.

6. Follow-Up Action

Each Competent Authority should have a written procedure to describe follow-up action to a rapid alert notification. The Competent Authority of each Member State and MRA partner to which a recalled product was exported should monitor the conduct and effectiveness of any national recall that it initiates as a result of the rapid alert notification.

The relevant Supervisory Authority should investigate the circumstances that led to the distribution of the defective product and ensure that any necessary corrective action is taken by the manufacturer and marketing authorisation holder as appropriate.

EMEA should co-ordinate follow-up action for recalls of centrally authorised products.

All follow-up actions transmitted through the Rapid Alert System should use the form for Follow-up and non-urgent messages for Quality Defects detailed in Appendix 3 to separate it from Rapid Alerts. It should have a reference number linking it to the original Rapid alert following the same format as described above.

7. Appendices

7.1. Appendix 1: Classification of Rapid Alerts
7.2. Appendix 2: Format for Rapid Alert Notification of a Quality Defect
7.3. Appendix 3: Format for Follow-up and non-urgent information for Quality Defects.

Appendix 1

Rapid Alert System : Classification of Urgency of Defective Medicinal Product Alerts

CLASS I

Class I defects are potentially life threatening or could cause a serious risk to health. These must be notified through the Rapid Alert System in all cases.

Examples:

- Wrong product (label and contents are different products)
- Correct product but wrong strength, with serious medical consequences
- Microbial contamination of sterile injectable or ophthalmic product
- Chemical contamination with serious medical consequences
- Mix-up of some products (rogues) with more than one container involved
- Wrong active ingredient in a multi-component product, with serious medical consequences.

CLASS II

Class II defects could cause illness or mistreatment, but are not Class I. These should be notified through the Rapid Alert System only to Member States and MRA partners to which it is likely or known that the batch has been distributed (including parallel import/distribution).

Examples:

- Mislabelling, e.g. wrong or missing text or figures
- Missing or incorrect information (leaflets or inserts)
- Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
- Chemical/physical contamination (significant impurities, cross-contamination, particulates)
- Mix up of products in containers (rogues)
- Non-compliance with specification (e.g. assay, stability, fill/weight)
- Insecure closure with serious medical consequences (e.g. cytotoxics, child- resistant containers, potent products).

CLASS III

Class III defects may not pose a significant hazard to health, but withdrawal may have been initiated for other reasons.

Examples:

- Faulty packaging, e.g. wrong or missing batch number or expiry date
- Faulty closure
- Contamination, e.g. microbial spoilage, dirt or detritus, particulate matter

Appendix 2

IMPORTANT - DELIVER IMMEDIATELY

Rapid Alert Notification of a Quality Defect / Recall

<table>
<tr><td colspan="4">[add title in national language if necessary]
[add letter head of sender]
[turn into bilingual model as required].</td></tr>
<tr><td colspan="4">1. To:
(see list attached, if more than one)</td></tr>
<tr><td colspan="3">2. Product Recall Class of Defect: I II
(circle one)</td><td>3. Counterfeit / Fraud (specify)*</td></tr>
<tr><td colspan="2">4. Product:</td><td colspan="2">5. Marketing Authorisation Number: *
For use in humans/animals (delete as required)</td></tr>
<tr><td colspan="2">6. Brand/Trade Name:</td><td colspan="2">7. INN or Generic Name:</td></tr>
<tr><td colspan="2">8. Dosage Form:</td><td colspan="2">9. Strength:</td></tr>
<tr><td colspan="2">10. Batch/Lot Number:</td><td colspan="2">11. Expiry Date:</td></tr>
<tr><td colspan="2">12. Pack size and Presentation:</td><td colspan="2">13. Date Manufactured: *</td></tr>
<tr><td colspan="4">14. Marketing Authorisation Holder: *</td></tr>
<tr><td colspan="2">15. Manufacturer†:

Contact Person:

Telephone:</td><td colspan="2">16. Recalling Firm (if different):

Contact Person:

Telephone:</td></tr>
<tr><td colspan="4">17. Recall Number Assigned (if available):</td></tr>
<tr><td colspan="4">18. Details of Defect/Reason for Recall:</td></tr>
<tr><td colspan="4">19. Information on distribution including exports (type of customer, e.g. hospitals): *</td></tr>
<tr><td colspan="4">20. Action taken by Issuing Authority:</td></tr>
<tr><td colspan="4">21. Proposed Action:</td></tr>
<tr><td colspan="3">22. From (Issuing Authority):</td><td>23. Contact Person:

Telephone:</td></tr>
<tr><td>24. Signed:</td><td colspan="2">25. Date:</td><td>26. Time: *</td></tr>
</table>

* Information not required, when notified from outside EU.

† The holder of an authorisation referred to under Article 40 of Directive 2001/83/EC or Article 44 of Directive 2001/82/EC and the holder of the authorisation on behalf of whom the Qualified Person has certified the batch for release in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC if different.

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Appendix 3

Follow-up and non-urgent Information for Quality Defects

	[add title in national language if necessary] [add letter head of sender] [turn into bilingual model as required].			
1	To: (see list attached, if more than one)			
2	Recall Number Assigned:	2a	National reference number (When applicable)	
4	Product:	5	Marketing Authorisation number:	
6	Brand/Trade name:	7	INN or Generic Name:	
8	Dosage form:	9	Strength:	
10	Batch number:			
14	Marketing Authorisation holder:			
15	Manufacturer[1]:	16	Contact Person:	
17	Subject title *Add bulk message here*			
22	From (issuing Authority):	23	Contact person:	
24	Signed:	25	Date:	26 Time:

[1] The holder of an authorisation to under Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC and the holder of the authorisation on behalf of whom the Qualified Person has certified the batch for release in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC, if different