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Management of rapid alerts arising from quality defects risk assessment

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Procedure for managing rapid alerts arising from quality defects risk assessment

1. Scope

This procedure covers the transmission across a "Rapid Alert Network" of a rapid alert notification when urgent action is required to protect public or animal health and covers both human and veterinary medicinal products

The rapid alert may be issued to:

Figure: 1. recall of one or more batches of a medicinal product suspected of having a quality defect

Figure: 2. recall of one or more batches of a medicinal product suspected to be falsified

Figure: 3. embargo or quarantine on the distribution of products following suspension or withdrawal of a manufacturing / wholesale authorisation.

Figure: 4. transmit information such as cautions-in-use, marketing authorisation withdrawals or suspension for safety reasons which may require recall of one or more batches of product from the market.

Figure: 5. notify quality defects, fraud or falsification in active pharmaceutical ingredients

Figure: 6. notify quality defects, fraud or falsification in investigational medicinal products

Figure: 7. follow-up messages to any of the above listed categories

The rapid alert is exchanged between:

Figure: 1. Competent Authorities in the European Economic Area (EEA) (the "Member States");

Figure: 2. EU acceding countries;

Figure: 3. Mutual Recognition Agreement (MRA) countries, as this procedure operates within the scope of the relevant "Two Way Alert" programmes established between the EU and MRA partners;

Figure: 4. Authorities participating in PIC/S;

Figure: 5. the European Commission;

Figure: 6. The European Medicines Agency (EMA);

Figure: 7. International organisations (Council of Europe/EDQM, WHO).

Pharmacovigilance or Medical Device alerts are not included within the scope of this procedure.

2. Introduction

2.1. Each holder of an authorisation referred to in Article 40 of Directive 2001/83/EC (for medicinal products for human use), Article 61(1) of Regulation (EU) No 536/2014 (for investigational medicinal products) or Article 88 of Regulation 2019/6 (for veterinary medicinal products) is required by Article 13 of Directive (EU) 2017/1572 (for human medicinal products), Article 14 of Commission Delegated Regulation (EU) 2017/1569 (for investigational medicinal products for human use) or Article 13 of Directive91/412/EEC (for veterinary medicinal 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.

2.2. In addition, for centrally authorised products, Council Regulation EC/726/2004, Article. 16(2) (for human products) or Regulation 2019/6, Article 58 (10) (for veterinary products), the marketing authorisation holder is obliged to inform the European Medicines Agency of any prohibition or

restriction of supply imposed by the competent authority of any country in which the medicinal product is marketed and of any new information which may influence the evaluation of the benefits and risks of the medicinal product.

2.3. In order to protect public health and animal health, EU authorities can avail of the "Rapid Alert System" which allows exchange of urgent information including urgent measures such as the recall of one or more defective batch (es) of a medicinal product during its marketing period or of an investigational product during clinical trials.

2.4. Each Competent Authority should have a written procedure for the issue, receipt, and managing of notifications of defective products, risk assessment of the quality defect, batch recalls and other rapid alerts 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 potentially concerned 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".

3. Definitions

3.1 **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.

3.2 **Quarantine**. Storage in separate areas, clearly marked and with access restricted to authorised personnel.

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 **Rapid Alert Network (RAN).** Network of competent authorities who exchange urgent information on quality defects and/or recalls related to medicinal products through the Rapid Alert System. RAN is composed by competent Authorities in the EEA, EU acceding countries, Mutual Recognition Agreement (MRA) countries, authorities participating in PIC/S, the European Commission and international organisations (Council of Europe/EDQM, WHO).

3.5 **Rapid Alert System (RAS)**. System in use amongst Authorities part of the Rapid Alert Network (RAN) to transmit alert on quality defects and/or recalls related to medicinal products whose urgency and seriousness cannot be delayed. The RAS includes also the "two-way alert" system established between the EU and MRA authorities.

3.6 **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

3.7 **Supervisory Authority**. Authority located in the country where the manufacturing facilities interested by the quality defect are located. These facilities could be the sites where the issue occurred or where the batch takes place.

3.8 **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.

3.9 **Suspected falsified medicine**. Any medicine with a false representation of its

Figure: 1. identity, including its packaging and labelling, and the name, composition and strength of any of its ingredients including excipients;

Figure: 2. source, including its manufacturer, country of manufacturing, country of origin and its marketing authorisation holder;

Figure: 3. history, including records and documents on distribution channels used.

3.10 **Withdrawal of marketing authorisation**. Interruption of placing on the market of the medicinal product by the marketing authorisation.

4. Criteria for issuing a rapid alert

4.1 The aim of the "Rapid Alert System" is to transmit urgent and serious alerts without any delay.

4.2 Before any Rapid Alert is issued to communicate a potential recall issue, a risk-based classification should be assigned to the rapid alert and the recall action if relevant. In this regard, the following should be noted:

Figure: 1. The classification assigned to a recall action and to a rapid alert should reflect case urgency and seriousness.

Figure: 2. In this context, the term 'urgency' relates to the urgency in taking a recall or other action in order to adequately protect patients, animals and users of medicines from the risks posed by quality defects in those medicines. When considering the 'urgency' of a recall action or a rapid alert, the risk-based classification that has been assigned to the quality defect report (High Risk, Moderate Risk, Low Risk) is taken into account. Refer to the procedure titled "Management and Classification of Reports of Suspected Quality Defects in Medicinal Products and Risk-based Decision Making "for more details in this regard, as well as Appendix 1 to that procedure.

4.3 There are three different risk-based classifications that may be assigned to a rapid alert (with or without a recall action) and to recall actions:

Figure: 1. Class I

Figure: 2. Class II

Figure: 3. Class III

The above risk-based classification is defined in Part III of Appendix 1.

4.4 The dissemination of the Rapid Alert takes into account the assigned class and also the countries effectively concerned by the batch (es) distribution.

5. Issue of a rapid alert notification

5.1. Responsibility

5.1.1. 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 (including mutually recognised or 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 (the issuing authority).

5.1.2. 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 occurred should lead the investigation of the defect and issue the rapid alert. If the defect occurred in a third Country, the Supervisory Authority identified by the EMA should lead the investigation of the defect and issue the rapid alert.

5.1.3. In the event of immediate danger to patients, animals, consumers or environment, the Competent Authority of the Member State where the defect was first identified should lead the

investigation and issue the rapid alert.

5.1.4. In both cases the alert should include a recommendation on proposed action (s) for all affected authorities.

5.1.5. In the case of centrally authorised products and when time allows, the content of the proposed action (s) should be agreed between:

Figure: 1. the Supervisory Authority,

Figure: 2. the Issuing Authority (if different from the Supervisory Authority),

Figure: 3. the European Medicines Agency and the CxMP rapporteur.

5.1.6. In some circumstances and especially when the Supervisory Authority has conducted all the required assessment, the Member State in which the defect was first identified may delegate to the Supervisory Authority the issuing of the Rapid Alert.

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

5.1.8. In the case of parallel distribution of a centrally authorised product and where no repackaging is done, the procedure described under 4.1.2 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 4.1.2 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 the European Medicines Agency.

5.1.9. 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.

5.2. Format of the rapid alert and its transmission

5.2.1. A suitable format for the notification of quality defects by the Rapid Alert System is given in Appendix 2.[1] The form should be completed clearly in English. The notification and relevant documents should be sent to the rapid alert contact list by electronic mail. The contact list and any relevant documents should be attached to the notification.

5.2.2. The electronic mail message should use a unique subject line to identify the rapid alert and any follow-up messages. The subject line should consist of the following:

<table>
<tr><th colspan="2">Type of rapid alert</th><th>Class</th><th>Medicine type</th><th>Product</th><th>Action</th><th>Reference number</th></tr>
<tr><td rowspan="3">RapidAlert</td><td>Qdefect</td><td rowspan="3">I
II</td><td rowspan="3">H or V</td><td rowspan="3">Name + INN</td><td>Recall</td><td rowspan="3">Country/Class/N°/N°</td></tr>
<tr><td>Falsified</td><td>No Recall</td></tr>
<tr><td>Fraud</td><td>Follow-up</td></tr>
</table>

Figure: 1. Example: RapidAlert; Qdefect; I, H; Product X; Follow-up, CH/I/07/01.

[1] The template can be downloaded at the following link: https://www.ema.europa.eu/en/human-regulatory/research- development/compliance/good-manufacturing-practice#compilation-of-union-procedures-section

5.2.3. The rapid alert should be given a unique reference number with the following format: Country code (country where the original alert was issued)/Region or Authority code (where applicable)/classification/year/sequential number/correspondence number. (For example, ES/II/2019/05/02 would indicate a class II rapid alert initiated by Spain, being the 5th rapid alert initiated by Spain in 2019 and that it is the second correspondence regarding this rapid alert.) The sequential number should reset every year.

5.2.4. Transmission of a Class I and, whenever feasible of a Class II, rapid alert must be concurrent with the national action and in all cases should be within 24 hours of the national notification.

In the case of a Class I alert, it may be necessary to notify authorities in different time zones in addition by telephone.

5.2.5. When an authority issues an additional rapid alert for a batch, the field 21 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.#".

5.3. Rapid alert contact list

5.3.1. The European Medicines Agency maintains the contact list for the rapid alert notifications of the competent authorities covered by Section 1. There is normally one contact per authority nominated by each member state. Changes to contact names or details must be notified to the European Medicines Agency (gdefect@ema.europa.eu) and are circulated immediately to the entire list by electronic mail. Contact details include telephone and fax numbers, electronic mail address, which should be monitored at all times.

6. Fraud and falsified products

6.1. It is acknowledged that the meaning of words such as "falsified" and "fraud" may vary from one country to another. It is also acknowledged that, in the European Union, the meaning of "falsified medicinal product" corresponds to the definition provided by Article 1 (c) of directive 2011/62/EU.

6.2. The Rapid Alert System should be used to notify competent authorities of the possible presence in the legal distribution network of falsified products or those resulting from fraud in manufacture, packaging, distribution or suspicious offer and products containing qualitative and/or quantitative different active substances than those described in the marketing authorisation.

6.3. The Competent Authority of the Member State or MRA partner in which the fraud or falsification was first detected should issue the Rapid Alert. The format for the rapid alert notification in Appendix 2 may be used, but the heading on the document should make clear that the notification relates to fraud or to a falsified product and sufficient information should be provided under "details of defect" to enable it to be identified. Notification should be sent to the entire Rapid Alert contact list.

7. Follow-up action

7.1. 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.

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

7.3. The European Medicines Agency should co-ordinate follow-up action for recalls of centrally authorised products.

7.4. 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 31 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.

8. Further use of rapid alert contact list

8.1. Although the contact list for rapid alert notifications shall be only used for the transmission of notification related to product quality defects GMP non-compliance procedure, in exceptional cases, if deemed relevant by the competent authority, the list may be used for the communication of other important and urgent information related to pharmaceutical products. These messages should clearly identify the subject and whether they are for information or action. For example, the European Medicines Agency disseminates urgent information from its scientific committees in this way.

9. Appendices

9.1. Appendix 1: Guidance in relation to the risk-based classification and decision making for quality defects, recalls, rapid alerts and risk reviews

9.2. Appendix 2: Format for rapid alert notification of a quality defect

9.3. Appendix 3: Format for follow-up and non-urgent information for quality defects

Appendix 1: Guidance in relation to the risk-based classification and decision-making for quality defects, recalls, rapid alerts and risk reviews

This guidance addresses the following four activities:

- Part I: Risk-based classification of quality defects
- Part II: Risk-based decision-making for quality defect cases to ensure that patients and animals are adequately protected from the risks presented by defective medicines
- Part III: Risk-based classification of recalls and rapid alerts
- Part IV: Risk Review of quality defect investigations

This guidance is intended for national competent authorities (NCAs) to assist them in their investigation of quality defect reports, and in their coordination and management of product recall and other risk reducing actions, as well as rapid alerts.

It is designed to reflect the principles and concepts of Quality Risk Management (QRM) as outlined in ICH Q9. In this regard, each of the four elements of QRM (*Risk Assessment, Risk Control, Risk Review and Risk Communication*) are addressed. For example:

- In Part I, the risk-based classification of quality defects can be considered an output of *Risk Assessment* activities.
- In Part II, the risk-based decision-making for quality defects results in actions that control risks for patients and animals, such as product recalls and the cessation of batch certification and release until the defect issue has been resolved. Such actions can be considered to be *Risk Control* activities.
- The outputs of Parts II and III, such as recall letters issued to healthcare professionals, and rapid alerts issued to other competent authorities, are types of *Risk Communication;* they provide timely information about potentially defective medicinal products on the market, so that risk mitigating actions can be taken to protect patients and animals.
- Part IV addresses the review of quality defect investigations and data to determine whether the key risks were actually identified and managed effectively; this is an example of *Risk Review* activities.

Each NCA is encouraged to use this guidance when working through its quality defect cases, in order to ensure a harmonised approach to the management of quality defects across the EEA.

Part I: Guidance in relation to the classification of quality defects

It is recommended that each quality defect case should be classified in accordance with the risks it may present to patients / animals. (This constitutes a risk assessment of the quality defect issue.) A classification should normally only be assigned after certain key information is gathered and after certain key questions have been considered. These are detailed below.

Following the receipt of a quality defect report, the NCA should work to understand and document the extent and the nature of the defect issue – an exact description of the defect should be obtained, and specific details about the medicinal product (or active substance, if the defect issue relates to an API) should be obtained. This includes the labelled product name, the pharmaceutical form, the product strength, the pack size, the batch number(s) and expiry date(s), the manufacturer(s), the authorisation status of the product, and whether it is a parallel imported / parallel distributed product.

Once information such as the above is known, the following key questions should be considered, to arrive at a risk-based classification of the defect:

1. In relation to the known extent of the defect:

Note: The questions below can be considered to relate to the likelihood of occurrence of the defect in the concerned product, and the following questions should be considered:

Considerations on the number of units/batches impacted:

- How widespread is the defect – is only one pack in one batch known to be affected, is the full batch likely to be affected, are multiple batches likely to be affected, are other strengths of the same product likely to be affected, etc.?
- Is the extent of the defect likely to increase throughout the remaining shelf-life of the batch? This may occur, for example, with stability-related quality defects.

Consideration on the distribution:

- How long has the defective batch and / or product been on the market?
- Have other quality defect reports been received at the NCA about the issue?
- Has the manufacturer / MAH received complaints from the marketplace about the defect?
- Has the manufacturer / MAH received any adverse reaction reports which could be related to the defect?
- To what level within the distribution chain has the defective batch reached, and how many units have been distributed?
- Are parallel imported / parallel distributed products and / or other products likely to be affected?
- Has the defective batch been distributed to any other market?

2. In relation to the nature of the concerned product:

Note: The questions below can be considered to relate to the intrinsic risk that is presented by the concerned product, and the following questions are designed to help understand that risk:

Considerations on medicines intended for human use:

Typology of product:

- Is it a non-sterile product or is it a product expected to be sterile? If sterile, is it terminally sterilised or aseptically prepared?
- Is it a cold-chain product?

- Is this a critical lifesaving / emergency treatment product, where there would be an acute danger to patient or animal health in the event of a quality defect (e.g. adrenaline injections, where a failure to deliver the dose could lead to patient harm)?
- What is the therapeutic class of the product? Is the product typically used for the long-term treatment of chronic diseases?
- Is the product an immediate release or a prolonged release formulation? (This can be important for stability and compositional-related quality defects.)
- Does the product have a narrow therapeutic index?

Typology of administration:

- Is the product self-administered or is it administered only by HCPs?
- Is the product complex to administer?
- What is the route of administration of the product - parenteral, oral, intrathecal, etc? Might this influence the risks presented by the defect?
- Does the defect pose a risk to those who administer the product – e.g. in case of accidental injection, inhalation, skin contact (e.g. cytotoxics), etc.?

Considerations on medicines intended for veterinary use:

- What is its criticality? For example, is it a non-critical product such as 'zootechnic' product (e.g. one used to manage female reproduction), or is it one that is considered clinically critical?
- Is the product given to food producing animals?
- Is the product used for mass herd / flock treatment, or to treat zoonotic diseases, or in disease eradication campaigns?

Other general considerations:

- Are there any indications that the quality defect issue might be the result falsification activities?

3. In relation to the patient groups potentially exposed to the defective units:

Note: The questions below can be considered to relate to the severity of the consequences of the quality defect on patients or animals.

- Are they high risk / vulnerable patient groups, such as neonates, immuno-compromised patients, children, etc.?
- Are the patients who use this product routinely monitored by a HCP?
- What is the general level of familiarity of patients in using the product?
- If it is a veterinary product, have the exposed animals a substantial value (e.g. racing horses, breeders, etc.)?

4. In relation to the quality defect itself:

Note: The questions below can be considered to relate to the severity of the consequences of the quality defect on patients or animals, or to the detectability of the issue.

Considerations on the harm posed by the defect:

- How might the defect be expected to cause harm / injury - might it lead to under-dose,

overdose, no dose, toxic effects, contaminants being ingested, administration errors, etc.?

- What is the likelihood that harm / injury may occur from exposure to the defective medicine?
- Is there a risk of harm to the person administering the defective product?
- Is there evidence that harm has actually occurred? Have any adverse reactions been reported that may be attributable to the defect issue?
- Is the defect readily detectable? (Caution – detectability should not be relied upon too much, because it is known that patients and HCPs still sometimes use defective products even when the defect is obvious and highly detectable.)
- What are the potential consequences of the defect? Illness, mistreatment / lack of treatment, lack of efficacy, infection, injury, death, no consequences, etc.?
- For veterinary medicines in food-producing animals, does the defect relate to the labelled withdrawal periods?

Other considerations:

- What is the risk posed to patients / animals if they do not take / receive the product?
- Does the defect relate to a non-compliance issue – such as the failure to implement a marketing authorisation variation, or a failure to comply with GMP? If yes, how serious is this failure?

Note: It is not intended that all of the above questions have to be addressed in every quality defect investigation – they are presented here as useful things to consider, but their relevance depends on the nature of the defect in question.

When the relevant questions above have been considered, the High / Moderate / Low Risk classification system outlined below should be used and a classification assigned to the defect issue.

Classification system for quality defects

High risk quality defects are defects which are potentially life-threatening or could cause serious risk to health.

Examples of such quality defects include:

- 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 or microbial contamination of any medicinal product which is administered to, or taken by, immuno-compromised patients or animals.
- Chemical contamination with serious medical consequences.
- Mix up of products ('rogues') within a pack. For example, two different blister strips within one outer carton, or, two different tablets within the one blister strip.
- Wrong active substance in a multi-component product with serious medical consequences.
- Serious adverse reactions which are batch or product related (most likely to be first notified to the Pharmacovigilance Department in an urgent safety report).
- The quality defect renders a life-saving product impossible to use, e.g. adrenaline, insulin, etc.
- The defect presents a high risk to those who may administer the product to patients or animals
- The defect presents a high environmental risk.
- Presence of particles in injectable medicinal products.

Moderate risk quality defects are defects which could cause illness or mistreatment with potentially non-serious medical consequences but are not classified as critical.

Examples of such quality defects include:

- Mislabeling issues - wrong or missing text or figures.
- Missing or incorrect information relating to labels, leaflets or pack inserts.
- Microbial contamination of products that are intended to be non-sterile, with potentially non-serious medical consequences.
- Chemical / physical contamination (significant impurities, cross-contamination, particulates).
- Mix up of products ('rogues'). For example, a case of product A contains one or more packs of product B) but A & B are very similar products (e.g. generic versions of a product) and the mix-up does not pose a clinical risk.
- Non-compliance with specification (e.g. assay, stability, fill / weight), with risk of lack of efficacy or toxicity. Note: certain lack of efficacy and toxicity issues might be considered to be high risk.
- Unsecured closure with non-serious medical consequences.
- Wrong withdrawal period for a veterinary medicine with moderate risk to animal-derived food products (e.g., milk, meat) – this would be where the withdrawal period is labelled as being shorter than that which is authorised.
- Significant OOT stability test results where batches on the market are likely to go out-of-specification before they expire.

Low risk quality defects are defects which are not likely to pose a significant hazard to health.

Examples of such quality defects include:

- Unclear labelling, minor labelling errors.
- Over-labelling of expiry dates or other information that is executed incorrectly.
- Faulty closures, where no increased risk to the quality of the product is presented.
- Wrong withdrawal period for a veterinary medicine with little or no potential risk to animal-derived food products (e.g. milk, meat) – this would be where the withdrawal period is labelled as being longer than that which is authorised.
- Under-filled or over-filled containers/packs which do not pose a clinical risk.
- Marginal OOS results at the end of the product shelf-life.

Note that the classification that is assigned to a quality defect issue is often largely influenced by the nature of the product concerned, and the classification may not always align with the above examples.

Non-justified quality defects are defect reports which could not be substantiated, and which were not true quality defects when they were investigated.

Examples of non-justified quality defects include:

- Reports in relation to the over-labelling on parallel import packs, when the over-labelling is actually in compliance with the parallel import authorisation.
- Reports of crystallisation in a product where crystallisation is a known phenomenon with that product and where the product information (e.g. package leaflet, Summary of Product Characteristics (SmPC), etc.) provides information on how to deal with that.
- Reports that relate to the misuse of the product.

Note: The High, Moderate and Low risk classifications are assigned to confirmed quality defect reports. The Non-justified classification is assigned to a quality defect report which, when investigated, is found not to be a confirmed quality defect. However, if there is any doubt as to whether the report is a valid report, a cautious approach should be taken, and it should be assumed that the report is valid. In such cases, the defect should be classified as a high, moderate or low risk quality defect.

The next part of this guidance relates to making risk-based decisions to ensure that patients and animals are adequately protected from the risks presented by defective medicines.

Part II: Guidance in relation to the risk-based decision making for a defect case to ensure that patients and animals are adequately protected

This part concerns decision-making that is designed to control and manage the risks that are presented by defective medicinal products. Different types of risk control actions may be taken in this regard (e.g. a product recall), but before they are considered, the following key questions should first be considered:

Considerations on the typology of defect and medicinal product:

- What classification has been assigned to the defect? (This is a general reflection of its seriousness.)
- Is the defect likely to exacerbate over time, potentially altering the risk posed by the defect throughout the remaining shelf-life of the batch? (This can be relevant to stability-related quality defects).
- If there is a clinical trial involved, is the risk presented by the issue sufficient to warrant a cessation of the trial?
- What is the method of sale and supply of the product?
- What is the remaining shelf-life of the defective batch?

Considerations on regulatory actions:

- If a recall action is being considered, how far into the distribution chain should it extend – to patient / user level, to pharmacies / hospitals only, to veterinarians, to wholesalers only, etc.? In other words, what type of recall action would be commensurate with the risks presented by the defect?
- What were the dates of first distribution of the defective batch (es) – is it likely that there are few, if any, packs of the defective product still remaining in the marketplace? What is the expected timeframe for any remaining units to become exhausted?
- Should an OMCL be asked to test or examine the product before a decision on market action should be made?
- If no market action is considered necessary, should the manufacturer be formally requested to cease the release of new batches of the product until it is assured that the defect issue has been addressed?
- Would it be appropriate to ask the manufacturer or wholesaler to inspect the packs under their control to identify any defective units and to allow them to market the remaining, defect-free packs?

Considerations on possible market disruptions:

- Is the issue so serious that a recall action justified even if it leaves the marketplace and patients with none of the medicine?
- If it is essential to ensure continuity of supply of the medicine, is there adequate replacement stock of defect-free product available to ensure this, in the event that the defective batch(es) is(are) recalled?
- Would the risks to patients / animals be higher if the product was not available versus leaving the defective packs in the marketplace?

- Is a therapeutically alternative product available and, if so, can patients / animals be switched to the alternative? (Note: Clinical expertise should be sought when considering this question.)

Considerations on communication to healthcare providers and/or patients:

- How readily detectable is the defect issue? (Caution – detectability should not be relied upon too much here, because it is known that patients and HCPs still sometimes use defective products even when the defect is obvious and highly evident.)
- Could the risks to patients or animals be adequately managed by a Caution-in-Use / Dear HCP Communication?

Having considered the above questions, a decision should be made as to what risk control action(s), if any, may best serve to manage the risks presented by the defective product, taking into account the need to be commensurate with the level of risk. (Note: NCAs are encouraged to discuss and communicate their risk-based decisions with other NCAs, where feasible.)

- 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, and it may be sufficient to direct the company to focus on the root causes of the defect and to ensure that effective CAPAs are implemented for it.

Part III: Risk-based classification of recalls and rapid alerts

Note: this guidance is intended to support the procedures in the Compilation of Union Procedures in relation to Rapid Alerts.

- It is recommended that each recall action and each rapid alert should be classified according to its urgency and seriousness.
- In this context, the term 'urgency' relates to the urgency in taking a recall or other action in order to adequately protect patients, animals and users of medicines from the risks posed by quality defects in those medicines.
- When considering the 'seriousness' of a recall action or a rapid alert, the risk-based classification that has been assigned to the quality defect issue – e.g. High Risk, Moderate Risk, Low Risk – should be taken into account.
- The following classification system should be used for recall actions and rapid alerts:
    - **A Class I rapid alert/recall action** relates to a potentially life-threatening issue. If a recall is required, it generally relates to high risk quality defect issues. When needed, they should extend to patient / user level, and cover all actors in the distribution network for the concerned product, e.g. all relevant wholesalers, retailers (pharmacies, veterinarians), clinics, etc., but the extent of the recall action depends on the extent of distribution of the defective product. A Class I rapid alert notification must be sent to all contacts of the rapid alert notification list irrespective of whether or not the batch was exported to that country.
    - **A Class II rapid alert/recall action** generally relates to an issue that could cause illness or mistreatment, but which does not warrant a Class I alert/recall. In case of recall, this generally relates to moderate risk quality defect issues. They should normally extend to pharmacy / retail level and cover all previous actors in the distribution network for the concerned product, e.g. all relevant wholesalers. Note that the extent of the recall action depends on the extent of distribution of the defective product. A Class II rapid alert notification should be sent to the rapid alert contacts of the countries to where the defective product was distributed. But, in cases where it is difficult to know where a batch has been distributed, the notification should be sent to all contacts in the rapid alert notification list. The potential for parallel distribution of the affected batch (es) should be taken into account when considering whether to send the rapid alert to all contacts in the rapid alert network.
    - **A Class III rapid alert/recall action** concerns an issue that may not pose a significant hazard to health. In this case a recall may be initiated for other reasons. Such recalls generally relate to low risk quality defect issues. They should normally extend to wholesaler level only. These are not notified through the Rapid Alert System.

Part IV: Risk review of quality defect investigations and related data

This Part addresses the review of quality defect investigations and their assessment to determine whether the key risks presented by the defective medicinal product were actually identified and managed effectively. Such risk reviews would be performed on a voluntary basis by Competent Authorities.

Each NCA should ensure that the following actions in this regard are performed:

- A sample of investigations concerning high risk quality defects, including Class I recalls and rapid alert cases, should be subjected to a formal risk review exercise.
- The risk review exercise should consider the following:
    - Whether the decisions made in the managing of those quality defect cases were adequate, taking into account all available information at the time;
    - Whether the risk-reducing actions that were taken at the time (if any) were commensurate with the level of risk that the quality defect presented to patients, users or animals;
    - Whether any risk acceptance decisions that were made at the time can still be considered to be justified;
    - Whether any new knowledge, experience or other information was received since the initial risk assessment which might alter the risk level that was determined for the quality defect issue at the time;
    - Whether any events occurred since the initial risk assessment that might impact the original quality risk management decision.
- The timing of such risk review exercises should be determined on a case-by-case basis, taking into account the level of risk that was estimated for the quality defect issue. It is suggested that high risk quality defect investigations should generally be reviewed within a period of 3-6 months after their receipt.

Appendix 2

IMPORTANT: DELIVER IMMEDIATLY- Rapid alert notification of a Quality Defect/Recall

"Confidential. For regulatory authority use only. Not intended for publication"

Add letter head of sender

1. Reference Number

2. Recall Number Assigned (if available)

+ -

Attach file

3. To: (see list attached, if more than one)

4.Files attached?

5. For use in | **6. Product recall/class of defect** | **7. Reason**

+ Product - Product

1

8. Product | **9. Strength** | **10. INN or Generic name** | **11. Pack size and Presentation**

12. Brand/Trade Name | **13. Dosage Form** | **14. Marketing Authorisation Number**

+ Batch - Batch

1.1

15. Batch Number (and bulk, if different) | **16. Date manufactured** | **17. Expiry Date**

18. Marketing Authorisation Holder

Name

Address

E-mail

Phone

19. Manufacturer

Name

Address

E-mail

Phone

20. Recalling Firm (if different)

Name

Address

E-mail

Phone

21. Site where the defect occurred (where the defect is attributed to a manufacturing site and if different from 19)

Name

Address

E-mail

Phone

22. Details of the Defect/Reason for the Recall

23. Information on Distribution including exports (type of customer, including parallel distribution/importation)

24. Action Taken by the Issuing Authority

25. Proposed Action

26. Issuing Authority

From (Issuing Authority)

Phone

Contact person

E-mail

Signature

27. Date/Time

Appendix 3

Follow-up and Non-urgent Information for Quality Defects

"Confidential. For regulatory authority use only. Not intended for publication"

Add letter head of sender	**1. National Reference Number (when applicable)**	
	2. Recall Number Assigned	

+ -

Attach files

3. To: (see list attached, if more than one)

4.Files attached?

+ Product - Product

1

5. Product

6. Strength

7. INN or Generic name

8. Brand/Trade Name

9. Dosage form

10. Marketing Authorisation Number

+ Batch - Batch

1.1 **11. Batch number (and bulk, if different)**

12. Marketing Authorisation Holder		**13. Manufacturer**	
Name		**Name**	
Address		**Address**	
E-mail		**E-mail**	
Phone		**Phone**	

14. Subject title

15.Issuing Authority Contact Person

From (Issuing Authority)

Contact Person

E-mail

16. Date/Time

Phone

Signature