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

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 / fraud 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 root cause(s) of the quality defect.

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 and/or wholesalers. Batch recalls may or may not be accompanied by withdrawal of a marketing authorisation.

3.2 **Quality defect report (QDR)/ Defective Product Report (DPR).** 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 (RA) 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 local/regional representatives, 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 also 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 within one working day (with justified exceptions) to a person(s) in charge of the preliminary risk-based assessment of the quality defect. Priority should be given to quality defects that are of most risk.

4.3 Levels of risk of quality defects and accompanying timelines

4.3.1 Quality defects should be handled by the NCA in a timely manner, commensurate to the level of risk the quality defect imposes on patients/animal health. This is meant as guidance for this purpose.

A risk-based classification of the defect should be performed within 1 working day of receipt of the report on condition that all information is complete. The risk assessment (if provided) and the guidance contained in Part I of Appendix 1 should be used to reach a risk-based classification. In cases where complete information is not available to classify the defect, a preliminary classification may be made. In these cases, where new information is provided, the provisional risk-based classification can be upgraded or downgraded according to the new evidence.

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

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

According to the level of risk, a deadline is established to initiate the QD management. The timings below should be considered as limits.

1. High Risk: 3 working days (Note: for issues with major public health impact, this timeline might be reduced to 1 working day)
2. Moderate risk: 5 working days
3. Low risk: 10 working days (optional timeline)

This management may include, among others, the following activities:

- contact the Marketing Authorisation Holder MAH or its legal representative to provide further information on the quality defect such as health hazard assessments, CAPA-plans, investigation report including the root cause analyses, as well as (preparatory) actions to be taken by the MAH.
- establish adequate provisional measures such us blocking/quarantine to limit the potential risk.
- Inform the concerned NCA's

4.3.3 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.

4.3.4 Some cases can be qualified as "non-justified" as explained in Part I of Appendix 1.

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

4.3.6 In order to promote harmonisation, the quality defect should also be classified using as far as possible a common standardised terminology (such as "non-justified", low-, medium- and high-risk QD).

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 three 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).

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 should be 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 II 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, among 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 Appendix 1 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 may include 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).

6. Appendices

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

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(R1). 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, as well as the guidance in ICH Q9(R1), in order to ensure that an appropriate degree of formality is applied when risk assessing, arriving at risk-based classifications for quality defect issues and when making decisions for risk-reducing actions. Efforts should also be made to ensure that the level of subjectivity that is associated with the risk assessments performed for quality defect issues is minimised. This facilitates a more 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 relate to the potential hazards presented by the defect and the severity of its consequences on patients or animals. They also relate 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 deciding how much effort and formality to apply when working to understand the four items listed above (the extent of the defect, the nature of the product, the patient groups potentially exposed to the defective units, and the potential harm posed by the defect issue), it is useful to consider the guidance in ICH Q9(R1) in the section titled 'Formality in QRM' and in the official training materials on this topic as published by ICH.

It is also important that efforts are made to minimise the level of subjectivity that is present when assessing the extent of the defect and the potential harm that may be posed by it. In this regard, it is useful to require the marketing authorisation holder (MAH) or the manufacturer of the product to provide objective data in relation to those items and to clearly provide mthe scientific basis of any estimates they make in relation to the extent of the defect and the potential harm that may be posed by it. Further guidance is available in ICH Q9(R1) in the section titled 'Managing and Minimising Subjectivity' and in the official training materials on Subjectivity in QRM as published by ICH.

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 with information for the patient and/or practitioners for example? (Note: The guidance in ICH Q9(R1) in relation to product availability risks is useful to consider.
- 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. When making such decisions, it is useful to consider whether a formal analysis of the available decision options should be undertaken. This can involve an in-depth consideration of the relevant factors associated with each option, including its advantages and disadvantages. When there is a high degree of importance associated with the decision, and when the level of uncertainty and/or complexity may be high, it is generally useful to perform such an analysis. Guidance in this area is provided in ICH Q9(R1) in the section titled 'Risk-based Decision-making' and in the official training materials on Risk-based Decision-making as published by ICH.

The main decision options and risk control actions that may be considered are listed below. This is not an exhaustive list.

(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: Urgency-based classification of rapid alerts

- It is recommended that each rapid alert should be classified according to its urgency and risk.
- 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 'risk' 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** 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** generally relates to an issue that could cause illness or mistreatment, but which does not warrant a Class I alert/ 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** 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.
- For useful information about Risk Review activities, see the official ICH Q9(R1) training materials on Risk Review as published by ICH.