IRISH MEDICINES BOARD

GUIDE TO REPORTING OF QUALITY DEFECTS IN MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

1. SCOPE

This guide covers the reporting to the Irish Medicines Board (IMB) of potential quality defects involving the following categories of medicinal products for human and veterinary use:

- Medicinal products which are the subject of a marketing authorisation (MA) or a registration for the Irish market,
- Medicinal products manufactured in Ireland for distribution outside of Ireland,
- Medicinal products which are neither authorised nor manufactured in Ireland, but which are distributed by Irish wholesalers or manufacturers,
- Promotional samples of medicinal products that are either manufactured in Ireland and/or are issued to Irish healthcare professionals,
- Exempt medicinal products for human use which are supplied to the order of a registered doctor or a registered dentist for use by his/her individual patients under his/her direct personal responsibility, or in the case of unauthorised veterinary medicinal products, supplied in accordance with the cascade system,
- Investigational medicinal products manufactured and/or distributed in Ireland for the purposes of performing clinical trials.

This is an industry guide for the following stakeholder groups:

- Marketing authorisation holders (MAHs)
- Registration holders
- Clinical trial sponsors
- Manufacturers
- Wholesalers

This guide does not cover products regulated under the Biocidal Products Directive or Medicated Feeding Stuffs Directive.

2. INTRODUCTION

A quality defect in a medicinal product may be defined as an attribute of a medicinal product or component which may affect the quality, safety and/or efficacy of the product, and/or which is not in line with the approved product authorisation (PA) or veterinary product authorisation (VPA) file, or other marketing authorisation. Reports of quality defects are received from a number of sources, such as manufacturers, pharmacists and members of the public. Certain stakeholders are required to report quality defects to the IMB, as per the following national Regulations:

Medicinal products for human use:

- Marketing authorisation holders and wholesalers of exempt medicinal products: S.I. 540 of 2007, as amended, the Medicinal Products (Control of Placing on the Market) Regulations 2007
- Manufacturers: S.I. 539 of 2007, as amended, the Medicinal Products (Control of Manufacture) Regulations 2007
- Wholesalers: S.I. 538 of 2007, as amended, the Medicinal Products (Control of Wholesale Distribution) Regulations 2007

Medicinal products for veterinary use;
- Marketing authorisation holders and manufacturers: S.I. 786 of 2007, European Communities (Animal Remedies) (No. 2) Regulations 2007.

For the specific sections of legislation above which are relevant to reporting quality defects and the related EU Directives, please refer to the IMB guidance note on Recall of Medicinal Products for Human and Veterinary Use, Appendix I.

When a quality defect is reported to the IMB, it is classified by the IMB according to its potential risk to patient safety and/or animal welfare and a decision is made on whether any market action is required to address the risk(s) presented by the quality defect. Depending on the classification assigned to the defect and the presence or absence of affected stock on the Irish market, the IMB may request the recall of the product or batch(es) of the product from the Irish market, or other market action(s) may be requested, as deemed necessary. Where the affected product is distributed outside Ireland, the IMB may inform other EU Member States' Competent Authorities (as well as the authorities of other countries) by sending a Rapid Alert notification to those countries.

As part of the concept of applying risk-based regulatory oversight as per the quality risk management principles of Annex 20 of the EU Guide to Good Manufacturing Practice, the IMB is providing this guidance so that stakeholders may be better able to determine which types of quality defects are required to be reported to the IMB and which ones are not.

3. CLASSIFICATION OF QUALITY DEFECTS

Classifying a quality defect is the first step to determining whether a defect is reportable or non-reportable. Suspected or confirmed quality defects may be classified into three categories, according to the risk posed to patient or animal health.

Critical quality defects are potentially life threatening or could pose a serious risk to patient or animal health.

Major quality defects are those which could cause illness or mistreatment but are not critical.

Minor quality defects are those which are unlikely to pose a risk to patient or animal health.

As a general rule, only minor defects should be considered non-reportable.

It is important to note that in some cases a serious non-compliance resulting in a quality defect, which the company has classified as a minor defect, may not result in a direct or significant increased risk to patients or animals; however, the non-compliance issue may be indicative of a wider problem within the relevant quality system. Market or other action may be required as a result of the serious non-compliance issue. In these cases, those non-compliances should be reported.

4. WHEN MIGHT A QUALITY DEFECT BE CONSIDERED NON-REPORTABLE?

All complaints and quality defect reports should be investigated by the MAH, manufacturer or wholesaler, regardless of their nature, and these investigations fully documented. Certain criteria should be used in order to determine whether a quality defect should be reported to the IMB or not. The defect should meet all the below three criteria in order to be considered as non-reportable:

(i) The defect is **minor** in nature, i.e. the increase in risk posed to patients or animals has been determined as low.

(ii) No market action is considered necessary by the company for the affected batch(es).
It is important to note that some minor defects do result in market action, such as the quarantine or recall of a batch or a number of batches. For example, minor packaging and/or labelling defects may in some cases be corrected by repackaging the affected units to bring those units into compliance with their marketing authorisation. If a repackaging operation occurs after the stock has left the control of the manufacturing site responsible for QP release of the batches, the action is classified as a recall by the IMB and such an action should be reported to the IMB, in advance of any repackaging being carried out.

(iii) The defect is isolated in occurrence.
A quality defect should only be considered non-reportable if it is determined that it is a minor defect which is not widespread throughout a batch or batches of a product, or in multiple products. If similar incidents are observed in other units of the same batch or indeed in other batches of the product, this should be treated as a more widespread quality issue and as such be reported to the IMB. Thus, it is important to maintain adequate records of all quality defects and perform trending of defects, regardless of whether the defect is classed as reportable or not. If an increased trend is observed in a defect which was not originally classed as reportable, consideration should be given to reporting the defect.

It is possible that there may be some exceptions, where the defect does not meet all the above criteria but may still be considered non-reportable. If it can be determined immediately that a defect is attributable to an external source, outside the responsibility of the MAH, manufacturer and/or wholesaler(s), it can be documented as not reportable. For example, a product which had deteriorated, having been kept outside its registered storage conditions at a retail premises or a patient's home, would not need to be reported once this had been confirmed and the correct storage conditions were clearly stated on the product labelling.

The same is applicable if the batch affected by the defect has not been QP-released and the defect is unlikely to have impacted other batches which have already been QP-released. If a batch is rejected due to a defect or deviation, the details should be documented as part of batch documentation as normal. This is not considered to be a quality defect. Such issues may be reviewed by inspectors at the next regulatory inspection at the company.

5. EXPECTATIONS OF COMPANIES WHEN NOT REPORTING QUALITY DEFECTS

It is expected that a quality defect report will always be investigated by the responsible stakeholder(s), whether the issue is confirmed as a true quality defect or not, as per Chapter 8 of the GMP Guide. The investigation should be fully documented and the issue should be documented or referred to during the product quality review for the product concerned, as necessary.

If preventative actions are identified during the course of the investigation, these should be implemented as normal. Investigation details and changes to procedures should be available for review during inspection of the manufacturing or wholesaling facility by a national Competent Authority, such as the IMB.

6. USE OF QUALITY RISK MANAGEMENT TO DETERMINE REPORTABILITY

In February 2008, the European Commission adopted the ICH Q9 Guideline on Quality Risk Management (QRM) into the GMP Guide as Annex 20. The document is aimed mainly at manufacturers, to be applied to their quality systems, but it can be applied to regulatory affairs or compliance-related activities within companies to determine whether a suspected defect should be reported.

There are four distinct parts to quality risk management: risk assessment, risk control, risk communication and risk review. Determining reportability should involve risk assessment and risk communication activities. Risk control and risk review will follow, but only as remedial measures after the defect has been reported.

Factors to consider when assessing the risk associated with a potential quality defect are:
- The potential consequences of the defect on patients or animals,
- The nature of the product involved (route and method of administration, therapeutic class, etc.),
- The nature of the patient population (or the most vulnerable of the patient population using the product),
- The risk posed by the patient not taking the product as a result of the defect.

7. CATEGORIES OF QUALITY DEFECTS

From year to year, the category of quality defects most frequently reported to the IMB relates to product packaging and/or labelling, followed by stability issues and product contamination reports. Other categories of defect include product usage issues, non-compliances with specifications, the presence of unlicensed product on the Irish market and others.

7.1 Quality defects that should always be reported

Certain types or categories of defect should always be reported to the IMB, as they are (potentially) serious in nature and have a high associated risk. These include:

7.1.1 Product mix-up issues

Reporting of a potential product mix-up is considered mandatory, as the administration of an incorrect product or an incorrect strength of a product to a patient could lead to serious situations such as overdose, underdose, allergic reaction or interaction with another contraindicated medicine.

7.1.2 Product contamination

The risk posed by a bacterial, fungal, viral, chemical or certain other types of contaminant can vary, depending on the contaminant involved (but often this may not initially be known) and the route of administration of the contaminated product (e.g. injectables). All contaminants should be viewed as potentially harmful.

7.1.3 Non-adherence to cold chain.

Cold chain involves the storage and transport of medicinal products, usually between 2° and 8°C. Any cold chain breach during the transport or storage of a product has the potential to adversely affect a medicinal product, potentially degrading the active substance and leading to a lack of potency or immunogenicity. Increases in impurities may also occur. Breaches of cold chain that occur at a manufacturing or wholesale facility and that are identified prior to product distribution past wholesale level do not need to be reported to the IMB. These issues should be managed and investigated via the company deviation process. Any breach of cold chain that is identified after a product has been distributed onward in the supply chain should be reported to the IMB.

7.1.4 Illegal or counterfeit product

A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to its identity and/or source (WHO definition). All suspected counterfeits should be reported to the IMB, so that the IMB can investigate and take precautionary measures if necessary.

7.1.5 (Potential) lack of sterility assurance

Defects that may affect the sterility assurance of a medicinal product, for example cracks in vials and leaking infusion bags, are deemed reportable, especially if the defect issue is not isolated in occurrence. Faults with containers or closures of sterile products can also cause a contamination risk or, if the product is harmful or toxic, a risk to the user or healthcare professional using the product.
Sterility assurance issues may also arise due to failed process simulation runs at a manufacturer or when sterilising equipment (such as autoclaves) has been found not to be operating correctly.

7.1.6 Unauthorised product on the market / unauthorised distribution

Any of the following can be classified as unauthorised products:
- A product which does not have an Irish product authorisation, an EU authorisation or an Irish registration and has not been distributed as an exempt medicinal product or via an approved batch specific request, but is considered a medicine by the IMB.

- A joint PA/PL product which has not been QP-released for the Irish market and does not possess a dual pack registration.
- A centrally authorised product which has an EU authorisation number but which has not been QP-released for the Irish market and does not have a parallel distribution authorisation.

The risks posed by unauthorised products may vary, depending on the information provided with the product and/or missing from the product packaging. These defects are considered reportable once the affected units have been formally entered onto a wholesaler's stock management system. If unauthorised product is identified during goods-in checks at pre-wholesale/primary wholesale level, and is not entered onto the stock management system of the wholesaler as a result, it does not need to be reported. Most reports of unauthorised products in Ireland involve UK-authorised products containing a PL or VM number only.

Unauthorised distribution of an Irish-authorised product is a reportable defect and includes:
- Distribution of medicinal products by a company or individual which does not possess a manufacturer's or wholesaler's authorisation issued by the IMB
- Distribution of medicinal products by, or to, a company or individual which is not authorised to distribute or receive them under the terms of the IMB manufacturer's or wholesaler's authorisation (for example, distribution of pharmacy-confined products by a grocery-only wholesaler or to a grocery-only retailer)

7.1.7 Stability issues

Since the introduction of the International Conference on Harmonisation stability requirements, the number of stability out-of-specification (OOS) results reported has risen. Stability issues can pose a risk to patient or animal health depending on the nature of the issue, but usually reports of a single OOS result do not result in any market action being required in Ireland. However, all confirmed OOS results are considered to be reportable to the relevant Competent Authority, as per Chapter 6 of the GMP Guide.

7.1.8 Non-compliance with specifications

Similar to stability OOS issues, non-compliances with finished product specifications (e.g. assay, preservative content, dissolution, related substances, etc.), which are identified when testing market or retained samples, may not pose any increased risk to patient or animal health, depending on the nature of the issue, the margin of failure and the nature of the product. For example, an assay failure in a batch of a product with a narrow therapeutic index would be viewed as relatively serious, while a similar failure in a product with a wider therapeutic index would likely pose a lower risk. Again, all non-compliances with finished product specifications should be reported, regardless of the perceived risk.

7.2 Quality defects that may or may not need to be reported

Other categories of defects could be considered reportable or non-reportable, depending on their nature. The criteria laid down in Section 3 above should be used as a guide along with the examples stated above, listed for each category, which are not exhaustive.

7.2.1 Packaging and/or labelling defects

Defects associated with product packaging and labelling constitute the highest proportion of reports received by the IMB. Medicinal products usually have multiple packaging and labelling components and can display large volumes of text, so there is the potential for a wide variety of defects to occur. These defects may not affect the product quality directly, but have an impact on the manner in which the product is prepared, administered or used.

The following **could** be deemed as non-reportable, following the criteria laid down in Section 3:

- Minor spelling error that would not cause any confusion or misunderstanding
- Incorrect text that would not cause any confusion or misunderstanding
- Missing label or leaflet (isolated incident) where the missing information is available elsewhere on/in the pack
- Missing tablet (isolated incident)
- Missing unit from a multi-pack (isolated incident)
- Missing or incorrect barcode, where the incorrect barcode does not relate to any other medicinal product
- Leaking container (isolated incident with a non-sterile product)
- Broken/crumbling tablets (isolated incident)
- Damaged carton/container (isolated incident)

7.2.2 Other non-compliances with marketing authorisations

Most other types of quality defects can be classed as a non-compliance with a product's marketing authorisation. As always, the risk posed by a defect should be evaluated before a decision is made on whether or not it is reportable.

In cases where the risk is unclear and therefore the reportability of a defect is difficult to determine, the stakeholder should contact the IMB (details below) to confirm whether the defect needs to be formally reported.

8. CONTACT DETAILS

Quality defects can be reported to the Quality Defects and Recall Group of the IMB in one of the following ways:

- Online, at www.imb.ie

- By e-mail, to recallsandqualitydefects@imb.ie

- By telephone, using the following contacts:

Ms. Aoife Farrell, Quality Defects and Recall Manager
Office contact no.: +353-1-676-4971
Out-of-hours contact details: Mobile +353-86-0249808

Ms. Breda Gleeson, Market Compliance Inspector
Office contact no.: +353-1-676-4971
Out-of-hours contact details: Mobile + 353-87-9703559

Mr. Rob Smyth, Market Compliance Technical Officer
Office contact no.: +353-1-676-4971

Mr. Kevin O'Donnell, Market Compliance Manager
Office contact no.: +353-1-676-4971
Out-of-hours contact details: Mobile + 353-87-9562818

Mr. John Lynch, Director of Compliance (out-of-hours only)
Out-of-hours contact details: +353-87-2347294