

Guide to Reporting and Initial Investigation of Quality Defects in Medicinal Products for Human and Veterinary Use



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1 SCOPE

This is an industry guide for the following stakeholder groups:

- marketing authorisation holders (MAHs)
- registration holders
- clinical trial sponsors
- manufacturers
- wholesalers

This guide covers the reporting to the Health Products Regulatory Authority (HPRA) 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 manufactured in Ireland for distribution to Ireland, but which do not possess an MA (compounded products)
- medicinal products which are neither authorised nor manufactured in Ireland, but which are distributed outside of Ireland by Irish wholesalers or manufacturers
- promotional samples of medicinal products that are either manufactured in Ireland and/or are issued to Irish healthcare professionals
- investigational medicinal products manufactured and/or distributed in Ireland for the purposes of performing clinical trials
- active substances used in the manufacture of medicinal products

Note: the following product types are within the scope of this guidance, but are also affected by other legislation and/or guidance:

Exempt medicinal products (EMPs) for human use

Reporting of quality defects involving EMPs, 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, is outside of the scope of this guidance, as stated in the [Guide to the notification system for Exempt Medicinal Products](#). Reporting of defects affecting EMPs is considered mandatory, due to the inability of the supplying wholesaler to fully investigate and gauge the extent of the suspected quality defect.

The contents of this guidance document can still be used to aid in the investigation of defects in EMPs.

Irish-manufactured products, authorised on other markets

The provisions of this guidance are applicable to Irish manufacturers but, where products are distributed by those manufacturers to other markets, those products may be subject to guidance applicable to those markets, as issued by the relevant competent authority.

Centrally Authorised Products (CAPs)

Although available in Ireland, CAPs are authorised by the European Medicines Agency (EMA). Quality defects involving CAPs are coordinated by the EMA and should be reported to the EMA, as necessary (please see [EMA website](#) for details). For quality defects affecting CAPs on the Irish market or manufactured in Ireland, the HPRA can be notified in parallel with reporting to EMA, using the guidance contained here. When submitting notifications in parallel, the EMA format for reporting can be used for both.

Active substances

As referenced in section 2 below, a legal obligation exists to report a defect with an active substance batch or batches but only '*in the event of a serious or potentially life-threatening situation*'. Therefore, the majority of this guidance document is not strictly applicable to active substance manufacturers. It should be noted, however, that under circumstances where the potential for a serious or life-threatening situation does exist, these defects should be reported to the HPRA. This does not supersede the reporting agreements in place between an active substance manufacturer and their customers. **Note: where the defective active substance has been used in the manufacture of finished product batches, already released to market, the rest of this guidance document applies, in the usual way, for the finished product manufacturer.**

This guide does not cover products regulated under the Biocidal Products Directive or Medicated Feedingstuffs 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 HPRA, as per the following national Regulations:

Medicinal products for human use:

- Marketing authorisation holders and wholesalers of exempt medicinal products: S.I. No. 540 of 2007, the Medicinal Products (Control of Placing on the Market) Regulations 2007
- Manufacturers: S.I. No. 539 of 2007, the Medicinal Products (Control of Manufacture) Regulations 2007
- Wholesalers: S.I. No. 538 of 2007, the Medicinal Products (Control of Wholesale Distribution) Regulations 2007

Medicinal products for veterinary use:

- Marketing authorisation holders and manufacturers: S.I. No. 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 [HPRA Guide to Recall of Medicinal Products for Human and Veterinary Use](#), Appendix I.

The sections of the above legislation generally state that a quality defect should be reported if it could result in '*a recall or abnormal restriction on supply*'. If this is the case, the decision on recall or other market action will be made in conjunction with the HPRAs.

For active substance manufacturers, the relevant legislation states that 'In the event of a serious or potentially life-threatening situation, local, national and/or international authorities should be informed and their advice sought' (as per [Part II of the EU Guide to Good Manufacturing Practice](#)).

This document provides additional guidance to that provided in the regulations above and in European legislation (for example the GMP Guide to Good Manufacturing Practice and the [EU Good Distribution Practice Guidelines](#)). The purpose of the guidance is to ensure that stakeholders are better equipped to report and investigate quality defects. The overall aims are:

- To ensure that potential quality defects are investigated and reported appropriately and in the required timeframes, to reduce, remediate or remove risk to patients or animals
- To ensure that the requisite oversight is applied to defect issues, commensurate with the level of risk posed to patients or animals

The HPRAs maintain oversight of investigations into quality defects on the Irish market, to assess the level of risk (risk classification, see below) and agree which market actions, if any, are required to mitigate against that risk. Apart from actions on the Irish market, communications may need to be sent to other affected competent authorities, to inform them of the defect issue. Lastly, HPRAs oversight may be required to oversee corrective and preventative actions at Irish manufacturing (for products distributed outside of Ireland), wholesale, regulatory or other facilities.

3 CLASSIFICATION OF QUALITY DEFECTS

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 and certain major defects may 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 INITIAL INVESTIGATION PHASE / INFORMATION GATHERING

In many cases, the classification, required action(s) and reporting requirements associated with a defect will be easy to determine immediately, for example an obvious quality defect, known to affect multiple units or batches. In some cases, these aspects will not be clear, usually where single or sporadic reports are observed or received from the market. It can be unclear if such cases represent a true defect issue or not. Either way, enough information should be gathered, to confirm:

- (i) If there is a risk to patient or animal health
- (ii) When and if the issue needs to be reported to HPRA
- (iii) If any market action is required
- (iv) If/ that there is a potential defect (i.e. that the complaint/report is justified)

There are two phases in assigning the criteria (i) to (iii), above, to a defect: gathering information on the defect and assessing its potential effects.

4.1 Information gathering

Before assessing the risk associated with a potential quality defect, as per section 4.2, a greater understanding of the defect should be gained. Information gathering can include such elements as:

- a full description of the defect and an examination of samples, if possible
- correspondence with the individual(s) who reported the defect, if applicable
- review of batch records and any change controls or deviations associated with the batch(es)
- review of previous complaints for the product/batch(es)

The final point above *may* reveal if:

- (i) The defect is isolated in nature and, therefore, may not need to be reported if the level of risk does not warrant it, or
- (ii) The defect is more widespread throughout a batch/batches and/or has the potential to lead to a shortage or recall; in such cases it should be reported. Full knowledge of the extent of a defect upon reporting it to the HPRA is helpful and can greatly speed up the investigative process.

Communication lines are vital to gathering the relevant information, for example:

- Medical information, complaints or customer service teams, for reports received from the market
- Contract manufacturers or laboratories, for stability out of specification/out of trend issues
- Communication between manufacturer and MAH for various incidents, deviations or MA non-compliances

4.2 Risk assessment

In February 2008, the European Commission adopted the [ICH Q9 Guideline on Quality Risk Management](#) (QRM) into the GMP Guide as a voluntary Annex. The document is not aimed solely at manufacturers; its guidance may usefully be applied by regulators and by MAH companies also, and it may be used to determine whether a suspected defect should be reported. Risk Assessment has been further incorporated into the GMP Guide, as part of Chapter 8, on Complaints and Product Recall.

Subsequent to or in parallel with initial investigation methods, the actual risk associated with the defect itself should be considered. Good information gathering can make risk assessment easier and less time-consuming.

There are four distinct parts to quality risk management: risk assessment, risk control, risk communication and risk review. Determining whether a defect should be reported should involve risk assessment and risk communication activities. Risk control and risk review will follow, but only as remedial measures, where necessary after the decision has been made on the reporting of the defect.

Factors to consider when assessing the risks associated with a potential quality defect include:

- the potential consequences of the defect on patients or animals
- the nature of the product involved (e.g. its route and method of administration, its therapeutic class, etc.)
- the nature of the patient population (or the most vulnerable of the patient populations) using the product
- the risk posed by the patient not taking the product as a result of the defect

5 DECISION ON REPORTING AND TIMELINES

Once initial investigations, as required, have described the defect, established its extent and classified the risk, it should be possible to determine when, and if, it should be reported to the HPRA, using the following guidance and approximate timelines in conjunction with section 7:

- All reportable defects should be reported as soon as possible, regardless of risk. If it is genuinely not possible to obtain the information in a timely manner, the HPRA should be consulted, to agree timelines and required actions, if any. If the information with which to report is available, unnecessary delays should be avoided.
- Critical or major defect issues which may lead to a recall should be reported immediately (as soon as reasonably possible). This is so that agreement can be reached on quarantine actions, recall level and availability of replacement stock, to limit the exposure of the defective batch. Before reporting, stock can be quarantined at the primary wholesaler, to minimise additional exposure.
- Minor or major issues where there is no proposed market action, but which are deemed reportable, should be reported in a timely manner. It is permissible to allow time for information gathering, but the amount of time spent doing so should be commensurate with the perceived risk. This could be a few days for potentially higher risk defects, to a maximum of around two weeks where the risk is lower. It is generally not considered acceptable to wait more than two or three weeks, or to complete an investigation before reporting.

Reportable quality defects should be notified by manufacturers, wholesalers and MAHs using the quality defect report (SUR-F0180). The information to be provided when reporting a potential quality defect is detailed in the Appendix. While details of the investigation performed to date should be included in the initial quality defect report, submission of the quality defect form should not be delayed pending completion of the root cause investigation.

A separate quality defect investigation report should be prepared upon completion of the company investigation to establish the root cause of the quality defect which includes the steps taken to investigate and to correct the source of the quality defect. Guidance on the requirements for quality defect investigation reports is available in the HPRA Guide to Quality Defect Investigation Reports (SUR-G0020).

6 ASSESSING A QUALITY DEFECT AS NOT REPORTABLE

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 or annual product 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 HPRA.

Certain criteria should be used in order to determine whether a quality defect should be reported to the HPRA or not. **The defect should meet all three of the below criteria in order to be considered as non-reportable:**

- (i) The defect is isolated in occurrence. A quality defect should only be considered non-reportable if it is determined that it is a 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 regarded as a more widespread quality issue and it should be reported to the HPRA. Thus, it is important to maintain adequate records of all quality defects and to perform trending of defects, regardless of whether the defect is initially 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.
- (ii) No market action is considered necessary by the company for the affected batch(es), as per the Regulations referred to in section 2, above. 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 recalling and repackaging the affected units to bring those units into compliance with their marketing authorisation.

Once a batch of product has been made available for sale at a wholesaler and, once that batch is retrieved due to a potential quality issue, this is considered a recall.
- (iii) The defect is considered **minor** in nature, i.e. the increase in risk posed to patients or animals by the defect has been determined as low or zero. Note: if a suspected defect is classified as major and if absolute assurance can be given that it is isolated, it need not be reported. If doubt exists over the classification of a defect or its extent, caution should be exercised and the defect reported.

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 non-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 investigation to confirm presence or absence of a defect should be performed in a timely manner and if this cannot be done, the suspected defect should be reported prior to this confirmation. Section 7 provides more guidance on sources and causes of defects.

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 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.

In situations where product on the market is found to be non-compliant with the marketing authorisation, there is no requirement to notify concerned competent authorities provided that the degree of non-compliance satisfies the restrictions regarding the handling of unplanned deviations laid out in Annex 16 of the EU GMP Guide (Certification by a Qualified Person and Batch Release).

7 CATEGORIES OF QUALITY DEFECTS

This section provides guidance on investigation and reporting of certain specific defect types. The list of categories of defects is not exhaustive and should be used as a guide only.

7.1 Product mix-up issues

A product mix-up is where the product name, as labelled and entire contents do not match, for example

- 10mg blisters, containing 10mg tablets, inside a carton labelled as 20mg.
- 10% v/v solution, in carton labelled as 10% v/v, but where bottle label states 5% v/v
- Ampoule containing product X, labelled and cartoned as product Y

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. Product mix-ups often involve multiple incorrect cartons, labels or blisters and usually lead to recall action, so one confirmed mix-up is considered a basis for reporting immediately.

When investigating product mix-ups, where incorrect packaging and/or labelling components are present, it is important to reconcile those components, to determine approximately how many packs or batches are affected. Review of line clearance activities, the primary cause of mix-ups, should be performed.

Where a pack contains a different batch number, but of the same product and strength, and both batches are genuine, i.e. not falsified, this should be investigated but is not deemed reportable, once the extent is low. Also, this only applies if both batches are in-date.

7.2 Rogue issues

Whereas a product mix-up is where the label and contents do not match, a rogue issue is defined as one or a small number of units, e.g. tablets or capsules, contained within a larger quantity of a different product or strength. This typically manifests as rogue tablets or capsules inside a container, with a different appearance to the main contents.

The investigation should be led by the manufacturer but should involve all potentially implicated sites, including bulk manufacturer. The first points to be established should be:

- (i) The identification of the rogue(s). If this cannot be done visually, then analytical testing should be undertaken.
- (ii) If the rogue(s) and main product are manufactured at a common site.

If it can be established quickly that the rogue(s) was not introduced at any stage during the manufacturing or wholesaling (returns) process, then the event does not need to be reported.

7.3 Product contamination

The risk posed by a bacterial, fungal, viral, chemical, physical or other types of contaminant can vary, depending on the contaminant involved (often this may not initially be known), the route of administration of the contaminated product (e.g. injectables) and the target patient population. All contaminants should be viewed as potentially harmful and suspected or confirmed contamination events reported without delay.

Testing is usually required to confirm the presence of a contaminant. As arrangement of testing and incubation and testing of samples can take some time, it is important that a parallel investigation, including batch review and complaint/defect history is performed. Where initial evidence points towards a contamination event, precautionary quarantine and informing the HPRA should be considered. Notification to HPRA of a precautionary quarantine, particularly due to potentially serious defect issues, should usually be done (this is applicable to all defect types).

It should be noted that a contaminant is a foreign substance which is not expected to be present in or on the product. Certain observations which may manifest themselves as contamination may not necessarily be so, for example precipitates, crystallisation or colour change. These are covered in a further section 'Non-compliance with specifications'.

7.4 Falsified medicines

A falsified medicine is one with a false representation of:

- (i) its identity, including its packaging and labelling, its name or composition as regards any of the ingredients including excipients and the strength of those ingredients;
- (ii) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or
- (iii) its history, including the records and documents relating to the distribution channels used.

All confirmed falsified medicines should be reported to the HPRA, so that the HPRA can investigate and take precautionary measures if necessary. This is where it has been confirmed, by inspection of a sample or photograph, review of documentation or analytical testing, that the sample meets one of the definitions above.

Where suspected falsification is identified, efforts should be made to obtain samples and gather information as quickly as possible. If it cannot be established quickly that there is no falsification, the issue should be reported.

Suspected falsification can arise from different scenarios. Product theft or diversion is not a reportable defect, but it can be associated with falsification, especially with certain susceptible product types. Suspected falsification can arise also in online and social media advertising where a prescription-only product may be misrepresented by a suspect falsified product. In the absence of a sample, it may not be possible to confirm the suspected falsification in the online advertisement. The HPRA's QDR section does not investigate distribution and supply outside of the legitimate supply chain, but it may want to inform other sections within the HPRA, so the above two scenarios are deemed reportable, for information, to compliance@hpra.ie.

Information on reporting quality defects associated with safety features is available in section 7.12.

7.5 Leakage/container-closure issues and sterility assurance

Leaks caused by a lack of integrity of containers of liquids are commonly observed, especially during product preparation and administration. Defects that may affect the sterility assurance of a medicinal product, for example cracks in vials and non-evident leaks in infusion bags, are deemed reportable. Faults with container closure systems for sterile products can represent a contamination risk or, if the product is harmful or toxic, a risk to the user or healthcare professional using the product, as well as to the patient or animal.

More evident leaks, where there is a low probability of the unit being administered (often administration is not possible where a gross leak has occurred) are not deemed reportable if it can be shown that the primary packaging, container/closure and product seals all functioned correctly. Where leaks have occurred in a hospital setting, samples can be difficult to obtain, so complaint trending is important.

7.6 Stability issues

7.6.1 General investigation

Stability samples and testing are seen as a representation of the product on the market, however, this correlation is not always accurate. For example, a stability batch might test well below specifications for assay or related substances, whereas units on the market meet specifications comfortably.

The primary purpose of stability out of specification (OOS) investigations should be to determine if there is a genuine stability issue with the product, by considering the following:

- Have previous OOS results been observed for the batch, the product, or other strengths of the product? Does the product have a poor stability profile or history?
- Do results for other parameters provide any information on the cause of the OOS?
- Is the product relatively new and, if so, do data from earlier time points or development / validation batches corroborate the observed OOS?
- Have any recent changes been made which would explain the OOS (i.e. if the batch has a different stability profile to previous batches)? Changes to review should include those to raw materials, manufacturing process, and packaging materials.
- If no explanation can be provided by initial investigation methods, consideration should be given to external factors which may have affected the stability samples only. Records to be reviewed should include:
 - o stability storage conditions (temperature and relative humidity logs)
 - o handling of stability samples
 - o stability testing or test method. Was the OOS confirmed or may it have been a testing anomaly?
 - o do the retain samples test within specifications? Retain testing is a very helpful method of investigation, for stability failures which might be caused or contributed to by the conditions in the stability chamber (assay, RS, LOD, hardness). Retain samples testing within specifications may not complete the investigation, but they can allow more accurate assessment of the quality of the product on the market and avoid potential market actions

7.6.2 Reporting

Stability issues can pose a risk to patient or animal health depending on certain factors, but usually reports of a single OOS result do not result in any market action being required in Ireland. However, all confirmed OOS or significant out-of-trend (OOT) results are considered to be reportable to the relevant competent authority, as per [Chapter 6 of the GMP Guide](#).

Reporting of stability OOS results to the HPRA should be considered as follows:

- 40°C/75% RH OOS results do not need to be reported if intermediate 30°C results are within specification. This is because 40°C studies do not represent any climatic zone, therefore are not an accurate indicator of product quality.
- 30°C OOS results should be reported, but only if the reference product is marketed in Zone III/IV countries and conditions apply to those countries. This applies to Irish manufacturers only where the product is distributed in Zone III/IV countries.
- If an OOS result is observed which is representative of product on the Irish market, it should be reported. This includes batches at the end of shelf life as, although market actions will not be required for the batch, other actions such as regression analysis for in-date batches and shelf life reduction may need to be considered.
- Subsequent OOSs for the same parameter (e.g. at different time points or for a different strength) should be reported, as the risk and decision on market action can change, depending on the new result.
- If the representative product is not manufactured in or marketed in Ireland or if the OOS does not represent Irish batches (i.e. the OOS applies to foreign batch/batches only) and the OOS is not indicative of a product-wide issue, then the OOS does not need to be reported.
- For validation or pilot batches, OOSs do not need to be reported as quality defects if they do not represent any marketed batch; however, consideration should be given to reporting to the relevant authority, if a commitment has been made to do so as part of an MA application or variation.
- If the OOS can be confirmed, in a timely manner, as being caused by a laboratory error, then it does not need to be reported. The laboratory error should, however, still be fully investigated.
- If the OOS is attributed to the test method itself, i.e. the test method gives false negatives, it should still be reported, as the QDR team may want to review potential changes to the test method, as CAPAs.

Stability OOT issues:

- OOT results, which indicate a likely future OOS, observed on stability should be reported if the batch or representative batch remains in-date on the Irish market (or relevant markets, for Irish-manufactured products). Extrapolation should be performed to determine if, and at what point, the batch will go OOS. The same investigative considerations should be made, as above.

OOS issues for active substance lots:

- There is no requirement in Part II of the GMP Guide for stability OOS issues relating to APIs, to be reported. Potential impact to the finished product should be considered, however, and the issue reported to the HPRA if potential impact is identified.

Delays in reporting are only deemed acceptable (minimal delays only) if an OOS or OOT is awaiting confirmation, e.g. a potential testing error. Otherwise, stability issues should be reported as soon as results and below supporting information are available.

Specific information to accompany a stability OOS/OOT notification (in addition to that stated in the Appendix):

- Stability conditions (e.g. 25°C / 60% RH)
- Stability time point
- Results obtained for the OOS/OOT parameter and all other stability parameters versus registered specifications
- Results of previous stability time points and results of release testing for the OOS batch
- Results of review of stability profile and previous/current stability issues for other batches or strengths (if time allows)
- Results of retain testing (if the OOS batch is in-date on the Irish market and if time allows)

7.7 Artwork and CMC MA non-compliances

Non-compliant artwork (carton, label, and leaflet) introduced by an error or due to incorrect implementation of a variation or MA transfer, is generally considered reportable. Release of a superseded artwork component, which was incorporated into a batch outside of the required timeframe (e.g. six months for certain variations), should be reported. If an error has been introduced to artwork which is very minor in nature, such as typos or omission of words, it can be considered acceptable not to report it and to update the artwork but, in general, the HPRA should be consulted before such a decision is made.

CMC (chemistry, manufacture, controls) non-compliances relate to the detail in the MA dossier itself. Examples of CMC non-compliances are those relating to manufacturing methods, starting materials and intermediates, raw materials and suppliers and in-process controls. Often, CMC non-compliances occur as a result of changes being made which are not reflected in the MA dossier, or variations to the MA which are approved and then not implemented.

If the CMC non-compliance results in failure to meet registered finished product specifications, or if an impact upon the quality, safety or efficacy of the batch cannot be ruled out, then the non-compliance should be reported. For deviations which are assessed not to have impacted upon the finished product, where finished product specifications have been met and where the requirements of [Annex 16 of the EU GMP Guide](#) (Certification by a Qualified Person and Batch Release) are adhered to, consideration can be given to not reporting the deviation and to the use of the Annex.

7.8 Non-compliance with specifications

Similar to stability OOS issues, non-compliances with finished product shelf-life specifications (e.g. assay, preservative content, dissolution, related substances, etc.), which are identified

when testing market or retained samples, may or may not pose an 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 usually be viewed as relatively serious, while a similar failure in a product with a wider therapeutic index would likely pose a lower risk. However, where product on the market is implicated, all confirmed non-compliances with finished product shelf-life specifications should be reported, regardless of the perceived risk.

As well as quantitative non-compliances with finished product specifications arising from testing, reports are commonly received of observed non-compliances with appearance specifications. Typically, these involve colour, precipitation/sedimentation and consistency/viscosity.

Often, it can be difficult to confirm if the appearance non-compliance represents a genuine defect or not. Outside of standard information gathering, it is important to consider at this stage:

- (i) Is the observation expected for this product/strength/dosage form?
- (ii) Might something have happened during storage, transport or use of the product?

On receipt of such reports and while awaiting samples, if available, for testing and analysis, photographs and retain samples can be checked. Early root cause analysis and early risk assessment are important and, unless it can be established in a timely manner that the defective unit does not represent the entire batch and that there is no significant risk, the defect should be reported.

7.9 Packaging and/or labelling defects

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 packaging and labelling 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, in accordance with 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)
- broken/crumbling tablets (isolated incident)

- damaged carton/container (isolated incident)

7.10 Non-adherence to cold chain

Cold chain involves the storage and transport of medicinal products at low temperatures, usually between 2°C and 8°C. Any cold chain breach during the transport or storage of a product has the potential to adversely affect the medicinal product, potentially degrading the active substance and leading to a lack of potency or immunogenicity and/or damaging the packaging of the product (which may then lead to contamination issues). Increases in impurities may also occur.

Not every cold chain breach needs to be reported. For breaches of a short duration and/or of a marginal nature, reporting is not usually necessary, if it can be shown that the breach has not adversely affected the quality of the product(s) involved. Data should be available to support such a position, including temperature studies performed on those products. For wholesalers, where such data are not readily available, it may be necessary to request a risk assessment from the relevant MAH to support a position of non-reporting. Cold chain issues that are not reported should be managed and investigated via the company's deviation process.

Some considerations are:

- Reporting should be decided by individual product assessment
 - o Storage conditions, e.g. 2–8°C vs. no registered storage conditions
 - o Likely effect on high/low temperature on product – is it biological / prone to precipitation
- Potential effect of freezing on the primary container should also be considered, e.g. cracking
- For investigations at wholesalers, assessments should be requested from the MAHs, where it is considered that the excursion is not minor.

If such justification cannot be obtained in a timely manner, all cold chain breaches should be reported.

7.11 Unauthorised product on the market / unauthorised distribution

Unauthorised products are defined as medicinal products that are available for sale on the Irish market without the appropriate authorisation or registration. They include:

- a product that does not have an Irish product authorisation, an EU authorisation or an Irish registration and has not been legally distributed as an exempt medicinal product, via the cascade system or via an approved batch specific request, but which is considered a medicine by the HPRA
- a product distributed under a dual product registration (DPR) which does not have a joint PA/PL pack

- a centrally authorised product which has an EU authorisation number but which has not been QP-released to the Irish market and which is not the subject of a parallel distribution authorisation from the EMA

The risks posed by unauthorised products can vary greatly in nature, and can sometimes depend on the information that is or is not provided with the product. Regardless of risk, these defects are considered reportable once the affected units have been formally entered onto an Irish wholesaler's stock management system. If unauthorised product is identified during goods-in checks at pre-wholesale/primary wholesale level, and if the product is not yet entered onto the stock management system of the wholesaler, the issue does not need to be reported. Most reports of unauthorised products in Ireland involve UK-authorized products containing a PL or VM number only.

Unauthorised distribution of an Irish-authorized product is a reportable defect and includes:

- distribution of medicinal products by a company or individual not in possession of a manufacturer's or wholesaler's authorisation issued by an EEA competent authority
- distribution of medicinal products by, or to, a person who is not authorised to distribute or receive them under the terms of the manufacturer's or wholesaler's authorisation (for example, distribution of pharmacy-confined products by a general sale wholesaler or to a general sale retailer)
- placement of a product on to a market for which the product is not authorised for sale and where such placement is not via the unlicensed supply route (equivalent of EMP supply in Ireland) for that market

Erroneous distribution of products is where the product is unintentionally distributed to an incorrect market, but a market where the product is authorised. This may be deemed not reportable, if:

- the distribution is to a market other than Ireland and the error occurred outside of the control of an Irish manufacturer or distributor (i.e. at a foreign distribution centre). Such a case should be reported to the national competent authority of the site where the error occurred.
- If the erroneous batch is detected at the wholesaler (be it in Ireland or elsewhere) before the batch is made available for sale.

Erroneous distribution can also include distribution of expired stock. If this is done by a wholesaler or distribution centre in Ireland, it should be reported, as follow-up will be needed in the form of a recall action and/or CAPAs.

7.12 Safety features

Suspected quality defects should be reported in the following situations:

- where there is reason to believe that the packaging of a medicinal product has been tampered with

- when the investigation of an alert by the MAH or its manufacturer results in an indication that the pack may not be authentic

The wording 'Safety Features' should be included in the e-mail subject header when submitting a quality defect form for a safety features issue.

8 CONTACT DETAILS AND HOW TO REPORT

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

- By e-mail (preferred method of reporting). Please complete the quality defect report form SUR-F0180 available from www.hpra.ie, save as a Word document and e-mail to qualitydefects@hpra.ie. The wording 'Safety Features' should be included in the e-mail subject header when submitting a quality defect form for a safety features issue.
- By telephone (for urgent issues), using the following contacts:

Dr. Amy Kelly, Quality Defects and Recall Manager
Office contact no.: +353-1-676-4971
Out-of-hours contact details: Mobile +353-86-0278052

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

Dr. 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

APPENDIX INFORMATION TO BE PROVIDED TO THE HPRA WHEN REPORTING A POTENTIAL QUALITY DEFECT

Product and batch details

- Product name, dosage, form, strength
- PA/VPA/PPA/DPR/CT/EU number for defects which affect Irish-authorized products
- Active substance(s)
- Manufacturer(s)
- MA holder for defects which affect Irish-authorized products
- Pack size(s)
- Batch number(s) and expiry date(s)
- Number of units in the batch(es)
- Dates of distribution of the batch(es), i.e. first/last dates of distribution to/from the primary wholesaler
- Markets to which the batch(es) were distributed and quantities that went to each

Description of the defect

- As full a description of the defect as possible (best obtained by inspection of defect samples, but can also include correspondence with the reporter, photographs)
- Outcome of examination and/or testing of retained sample, where appropriate
- Number of similar complaints/issues identified for the batch or product (all markets)
- Confirmation of review of batch records, historical data and any relevant findings identified
- Review of previous complaints, investigations, if applicable
- Date when defect was first identified
- Summary of the main findings to date of the investigation performed