HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Reporting and Investigation 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.

CONTENTS

ABBREVIATIONS

API is active pharmaceutical ingredient
CAP is centrally authorised product
CAPA is corrective and preventive action
CMC is chemistry, manufacturing, controls
EMP is exempt medicinal product
EU is European Union
GMP is Good Manufacturing Practice
HPRA is the Health Products Regulatory Authority
MA(H) is marketing authorisation (holder)
OOS is out of specification
OOT is out of trend
PA is product authorisation
QD is quality defect
QDR is quality defects and recalls
RCA is root cause analysis
RH is relative humidity
SA is supervisory authority
VPA is veterinary product authorisation

1 INTRODUCTION

A quality defect in a medicinal product may be defined as an attribute of a medicinal product, or component, affecting the quality, safety and/or efficacy of the product, and/or which is not in line with the approved product authorisation (PA), veterinary product authorisation (VPA), or other marketing authorisation.

Reports of quality defects are received from a number of sources including other competent authorities, MAHs, manufacturers, pharmacists, other healthcare professionals and members of the public.

Reports to the HPRA should relate to product placed on the Irish market or products manufactured at Irish wholesale or manufacturing sites for products distributed outside of Ireland.

Stakeholders are required to report quality defects to the HPRA, as per legislation outlined in Appendix 1 of this guide, which generally states that a quality defect should be reported if it could result in '*a recall or abnormal restriction on supply*'.

The decision on whether a recall or other market action is warranted should be made in conjunction with the HPRA (see the HPRA's Guide to the Recall of Medicinal Products for Human and Veterinary Use available on the HPRA website).

The purpose of this document is to provide additional guidance to that contained in the legislation, to ensure that stakeholders:

(i) Report and investigate potential quality defects appropriately and in the required timeframes, to mitigate risk to patients or animals.
(ii) Apply requisite oversight to defect issues, commensurate with the level of risk posed.
(iii) Carry out detailed root cause analysis (RCA) investigations to ensure appropriate corrective and preventive actions are implemented, to prevent recurrence of issues leading to the quality defect.

The HPRA maintains oversight of quality defect investigations and market actions.

Communications may also be sent by the HPRA to other affected competent authorities to inform them of the defect issue.

2 SCOPE

This is an industry guide for the following stakeholder groups:
- marketing authorisation holders (MAHs)
- product registration holders

- clinical trial sponsors
- medicinal product and active substance manufacturers
- medicinal product wholesalers

This guide covers the requirements for investigating and reporting to the HPRA quality defects in the following categories of human and veterinary medicinal products:

- medicinal products subject to a marketing authorisation (MA) or registration for the Irish market
- medicinal products manufactured in Ireland for distribution outside of Ireland
- medicinal products manufactured in Ireland for distribution within Ireland, but which do not possess an MA for Ireland (e.g. unlicensed compounded products)
- 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
- 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
- exempt medicinal products (EMPs)

The following product types are within the scope of this guidance, but may also be impacted by other legislation and/or guidance:

Irish-manufactured products, authorised on other markets

Where products are distributed by Irish manufacturers to other markets, those products may also be subject to quality defect reporting guidance applicable in those other markets, as issued by the relevant competent authority.

Centrally authorised products (CAPs)

CAPs are authorised by the European Commission. Quality defects involving CAPs are coordinated by the EMA and should be reported directly to the EMA through their website at www.ema.europa.eu.

Active substances

An obligation exists to report a defect with an active substance batch or batches *'in the event of a serious or potentially life-threatening situation'* (as referenced in Part II of the EU Guide to Good Manufacturing Practice).

Outside of scope

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

3 INITIAL INVESTIGATION PHASE

Where a quality defect is suspected or identified by a company, sufficient information should be gathered to determine whether a quality defect is reportable to the HPRA.

The initial assessment of whether a defect is reportable should address:
- whether the report or complaint is justified
- what level of risk, if any, is posed to patient, user or animal health
- the extent of the issue (impact on other batches/products)
- if potential market action (e.g. recall, caution-in-use notification) is warranted
- whether the defect could result in a restriction in supply or a shortage of the product

4 RISK IN RELATION TO QUALITY DEFECTS

4.1 Risk assessment

Factors to consider when assessing the risks associated with a potential quality defect include:
- the potential consequences of the defective product(s) for patients, users or animals
- the nature of the product(s) involved, e.g. route of administration, therapeutic class
- the nature of the patient/animal population (especially vulnerable patient populations)
- the risk(s) posed by the patient/animal in not taking the product(s) as a result of the defect

4.2 Classification of quality defects

Quality defects may be classified into three categories, according to the risk posed to patient, user or animal health:

High risk (critical) quality defects - potentially life threatening or could pose a serious risk.
Examples include:
- falsified product
- wrong product (label and contents are different)
- correct product but wrong strength, with serious medical consequences
- microbial, physical or chemical contamination, with serious medical consequences
- mix-up of products ('rogues') within a pack
- wrong active ingredient in a multi-component product with serious medical consequences
- quality-related serious adverse reactions which are batch or product specific (these are most likely to be first notified to the Human Products Monitoring department of the HPRA)

Moderate risk (major) quality defects - could cause illness or mistreatment but not to a life-threatening extent.
Examples include:
- mislabelling (incorrect or missing text or figures)
- missing or incorrect information on leaflets or inserts

- microbial, physical or chemical contamination, with medical consequences
- non-compliance with release/shelf-life specification (e.g. assay, fill/weight, related substances)
- insecure closure with medical consequences (e.g. cytotoxics, ineffective child-resistant containers, potent products)

Low risk (minor) quality defects - unlikely to pose a risk to user, patient or animal health. Examples include:
- faulty packaging, e.g. wrong or missing batch number or expiry date
- faulty closures (non-sterile products)
- microbial, physical, or chemical contamination unlikely to have medical consequences

5 QUALITY DEFECT REPORTING

Where a potential quality defect has been identified which may result in a market action or in an abnormal restriction in supply, the HPRA should be notified of the quality defect in a timely manner, as per EU GMP Guidelines – EudraLex Volume 4, Chapter 8 (Complaints and Product Recall).

Note: There is no requirement to notify the HPRA if the degree of the non-compliance would have satisfied EU GMP Guidelines, Section 3 of Annex 16 (Certification by a Qualified Person and Batch Release), were the non-compliance identified prior to certification and release of the batch. Such a non-compliance, however, should not represent a wider problem, which impacts marketed products.

In some cases, a serious non-compliance with the marketing authorisation or with GxP may arise, which may not lead to a direct or significant increased risk to patients, users or animals. It should always be considered whether the specific non-compliance issue is indicative of a wider problem within the relevant quality system which, in its entirety, may result in a need for market or other action. In such cases, these non-compliances should be reported.

Reporting of QD issues is **mandatory** in the following instances:
- all quality defects that could result in a recall or in an abnormal restriction on supply
- unauthorised product on the market/unauthorised distribution
- unauthorised distribution of an Irish-authorised product
- erroneous distribution of expired product
- defects in EMPs (all quality defects in EMPs are reportable)
- certain out-of-specification (OOS) and significant out-of-trend (OOT) stability test results – see Appendix 2 – Stability Issues section of this guide for details
- a defect in an active substance batch or batches 'in the event of a serious or potentially life-threatening situation'

Appendix 2 provides topic specific guidance to assist the assessment of the obligation to report to the HPRA.

6 COMPILATION OF UNION PROCEDURES

The European Commission has published a set of documents followed by GMP Inspectorates known as the 'Compilation of Union Procedures on Inspections and Exchange of Information', or Compilation of Union Procedures.

While these procedures are not directly aimed at marketing authorisation holders or manufacturers, two specifically relate to quality defects, i.e. 'Management and classification of reports of suspected quality defects in medicinal products and risk-based decision-making', and 'Procedure for managing rapid alerts arising from quality defects risk assessment'.
An associated appendix provides useful and detailed guidance on the application of Quality Risk Management principles to quality defect investigations and risk-based decision making (see 'Procedure for managing rapid alerts arising from quality defects risk assessment', Appendix 1: Guidance in relation to the risk-based classification and decision-making for quality defects, recalls, rapid alerts and risk reviews). It also addresses the risk-based classification of quality defects. These documents complement the guidance in relation to quality defect handling and decision making in Chapter 8 of the EU GMP Guide - Complaints, Quality Defects and Recalls.

Marketing authorisation holders and medicines manufacturers are encouraged to review these documents.

7 HOW TO REPORT A QUALITY DEFECT TO THE HPRA

Once the requirement to report has been established, manufacturers, wholesalers and MAHs should report quality defects to the HPRA by completing the quality defect report form (SUR-F0180) found on the HPRA website, under Report an Issue.

The report should be submitted in Word format, by email to qualitydefects@hpra.ie.

While details of the investigation performed up to the point of reporting may 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.

Urgent and high-risk quality defect issues may also be initially reported to the Quality Defects and Recall group of the HPRA by telephone using the contacts shown in Appendix 3 of this guide.

Report requirements

The following details should be provided when reporting a quality defect:

Product and batch details

- Product name, dosage, form, strength
- PA/VPA/PPA/DPR/CT/EU number for defects which affect Irish-authorised products
- Active substance(s)
- Manufacturer(s)
- MA holder for defects which affect Irish-authorised 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 Irish 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 and 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
- An assessment of risk, extent and potential market impact

Specific information to accompany a stability OOS/OOT notification:

- Stability storage conditions (e.g. 25°C/60% RH)
- Stability time point impacted (e.g. 6 months, 12 months, etc.)
- Results obtained for the OOS/OOT parameter and results for all other stability parameters *versus* the registered specifications
- Results of previous stability time points and results of release testing for the OOS batch
- Results of review of the product stability profile and previous/current stability issues for other batches or strengths (if time allows)
- Results of reference (retained) sample testing (if the OOS batch is within its expiry date on the Irish market)

8 REPORTING TIMELINES

All reportable defects should be notified to the HPRA as soon as possible, regardless of risk. If it is genuinely not possible to obtain the required information in a timely manner, the HPRA should be consulted to agree timelines and required actions, if any.

- **High risk (critical) and moderate risk (major) defect issues** should be reported immediately (maximum three days). Before reporting, stock can be quarantined at the primary wholesaler, to minimise additional risk, if appropriate.

- **Low risk (minor) or moderate risk (major) issues where there is no proposed market action** should be reported to the HPRA in a timely manner (moderate risk – maximum five working days, low risk - maximum ten working days).

9 DECISIONS ON MARKET ACTION

Where a quality defect is deemed to warrant market action this will be discussed and agreed with the responsible party and the HPRA.

Market action may include a product or batch quarantine, recall to wholesale, retail or patient/user level, and/or issuance of communication to healthcare professionals (e.g. caution-in-use notification)

For more information please see the HPRA's Guide to the Recall of Medicinal Products for Human and Veterinary Use available on the HPRA website.

10 FINAL INVESTIGATION REPORT

The relevant MAH, manufacturer and/or wholesaler is required to initiate an investigation to establish the extent and root cause(s) of the defect, and to propose corrective actions to prevent a recurrence.

The HPRA may request a formal investigation report, especially where the risk is classified as high (critical) or moderate (major). The expected timeframe for submission of the investigation report to the HPRA is **four weeks**. If the investigation cannot be completed within this timeframe, a modified timeframe may be agreed in advance with the HPRA. The report should describe the steps taken during the investigation and actions taken/proposed to correct and/or prevent reoccurrence of the defect.

The overall responsibility for preparing and submitting the investigation report normally rests with the MAH (if there is one), although the MAH may delegate this action to the manufacturer.

In cases where the source of the defect is identified at a wholesaling facility, the HPRA may request the investigation report directly from the wholesaler.

For a quality defect relating to an exempt medicinal product, the company that submitted the notification of placement of the product onto the Irish market (this is usually a wholesaler) is responsible for submitting the investigation report.

Where the quality defect leads to a recall action, a separate quality defect investigation report is not required, as the relevant information will be submitted to the HPRA in the recall report (see the HPRA's Guide to the Recall of Medicinal Products for Human and Veterinary Use).

Required format for quality defect investigation reports

A quality defect investigation report should contain:

An **executive summary** to provide a brief high-level overview of the quality defect issue and any market actions taken.

A section on **investigation details**, which should include, where applicable:
- exact product name
- batch number(s) affected and expiry date(s)
- active substance name(s)
- product strength(s)
- pharmaceutical form (e.g. tablets, powder for solution for infusion)
- description of the product (e.g. tablets in polyethylene tub, blisters in carton)
- pack size (e.g. 28s)
- marketing authorisation (PA/VPA/EU) number(s), parallel import (PPA) number(s), or product registration number(s)
- name and address of the QP-release site
- name and address of Irish manufacturer(s) involved in any stages of manufacturing
- name and address of the primary wholesaler in Ireland
- details of other markets to which the affected batch(es) was/were distributed
- total quantity of packs manufactured for the affected batch(es)
- total quantity of units from the affected batch(es) distributed on the Irish marketplace
- date the quality defect issue was first discovered by the MAH or manufacturer
- date the quality defect issue was reported to the HPRA

(Some of this information may have been previously provided in the quality defect report, which can be attached as an Appendix.)

The report should also include:
- a comprehensive description of investigation carried out
- risk classification and justification for the classification
- root cause(s) of the quality defect
- extent of the quality defect (e.g. number of packs affected per batch)

- details of corrective and preventive action(s) arising from the investigation, and a timeline for the completion of each CAPA identified
- planned completion date(s) for outstanding corrective and preventive action(s)

The report may also include other information such as health hazard assessments, as appropriate.

11 REFERENCES

1. EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines
   - Chapter 6: Quality Control
   - Chapter 8: Complaints, Quality Defects and Product Recalls
   - Annex 16: Certification by a Qualified Person and Batch Release

   https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

2. Compilation of Union Procedures on Inspections and Exchange of Information
   - Management and classification of reports of suspected quality defects in medicinal products and risk-based decision-making
   - Procedure for managing rapid alerts arising from quality defects risk assessment

   https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-manufacturing-practice/compilation-union-procedures-inspections-exchange-information

3. Alert Management Guidance pertaining to Safety Features relating to the Falsified Medicines Directive (Alert Management Guidance - IMVO)

Note: MAHs, manufactures and wholesalers are requested to review the above guidance and to follow the reporting requirements within.

APPENDIX 1 LEGISLATION

In relation to medicinal products for human use:

- **Marketing authorisation holders and wholesalers of exempt medicinal products:** the Medicinal Products (Control of Placing on the Market) Regulations 2007-2019, as amended

- **Manufacturers**: the Medicinal Products (Control of Manufacture) Regulations 2007-2022, as amended

- **Wholesalers**: the Medicinal Products (Control of Wholesale Distribution) Regulations 2007-2021, as amended

In relation to medicinal products for veterinary use:

- **Marketing authorisation holders, manufacturers and wholesalers:** European Communities (Veterinary medicinal product and medicated feed) Regulations 2022 (S.I. No. 36 of 2022)

APPENDIX 2 CATEGORIES OF QUALITY DEFECTS

This section provides guidance on reporting of certain defect types. The list of categories of defects is not exhaustive and is intended as a guide only.

Falsified medicines and safety features

A falsified medicine is one with a false representation of:
- 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;
- its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or
- its history, including the records and documents relating to the distribution channels used.

Falsification may be confirmed through inspection of a sample or photograph, or via the review of documentation or the results of analytical testing and should be reported to the HPRA immediately - as soon as falsification is confirmed (or at most within 24 hours).

In cases of suspected falsification, 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, in isolation, 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 suspected 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 may want to inform other sections within the HPRA, so the two scenarios above are deemed reportable, for information, to compliance@hpra.ie.

In relation to packs of medicines that give rise to safety feature alerts when their 2-D barcodes are scanned, only those cases which have been investigated by the MAH or manufacturer and determined to be confirmed falsification cases should be reported to the HPRA as quality defects.

Safety features

Suspected quality defects should be reported immediately 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 a safety features alert by the MAH or its manufacturer results in confirmation that the pack with the alert is a falsified pack or there is an indication that the

pack may not be authentic. Further information is available from the IMVO Alert Management Guidance.

Product mix-up issues

A product mix-up is where the product name and/or strength, as labelled, and the pack contents do not match.

Where it cannot be ruled out that a product mix-up occurred under the manufacturer's control, reporting of the defect to the HPRA is considered mandatory, as the administration of an incorrect product/strength of a product 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.

Where a manufacturer can quickly rule out that the product mix-up occurred at any stage during the manufacturing or wholesaling (returns) process (e.g. a blister strip of tablets was put into an incorrect outer carton within a pharmacy or at a patient's home), the issue is not considered reportable.

If the manufacturer cannot quickly rule out that the mix-up occurred within their control, the HPRA should be notified of the issue within two to three days, while the investigation is ongoing.

Rogue issues

While a product mix-up issue is one where the label and contents do not match, a rogue issue is where one or a small number of units, e.g. tablets or capsules, are found to be contained within a larger quantity of a different product or strength. This typically manifests as a number of '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 the bulk product manufacturer. The first points to be established include:

(i) the identification of the rogue(s), visually or through analytical testing
(ii) determination as to whether the rogue(s) and main product are manufactured/packaged at a common site

If it cannot be ruled out that the introduction of the rogue units occurred within the control of a manufacturer (e.g. via ineffective packaging line clearance processes) the defect should be reported to the HPRA within two to three days, while the investigation is ongoing. If it can be quickly established that the rogue units were not introduced at any stage during the manufacturing or wholesaling (returns) process, then the issue does not need to be reported.

Sterility assurance – media fill issues

Manufacturing issues which may have an impact on the sterility of a product (e.g. failed media fills) should be notified to the HPRA within 24 hours.

Sterility assurance - leakage/container-closure issues

Defects that may affect the sterility assurance of a medicinal product (e.g. cracks in vials and pinhole or non-obvious leaks in infusion bags) are deemed reportable.

More evident leaks, which are isolated in occurrence and/or where there is a low probability of the unit being administered (e.g. administration is not possible where a gross leak has occurred) are not deemed reportable.

Faults with container closure systems, where the product is harmful or toxic, pose a risk to the user or a healthcare professional using the product, as well as to the patient or animal. This should be considered in the risk assessment and investigation.

Stability issues

The EU GMP Guidelines Chapter 6 (Quality Control) address the reporting of confirmed out-of-specification (OOS) and significant out-of-trend (OOT) test results from ongoing stability studies.

All confirmed OOS and significant OOT stability test results are reportable to the HPRA where the stability test conditions are representative of market conditions and one or more of the following criteria are met:

- where the OOS/OOT batches are on the Irish market or are representative of batches currently on the Irish market and for which market action may be required.
- where the OOS/OOT batches are not on the Irish market nor representative of batches currently on the Irish market, but the HPRA is supervisory authority and market action may be required in a market other than Ireland.

Note: The testing of a reference (retained) sample of a batch with an OOS/OOT stability test result is a useful part of the investigation into those issues, and such testing may be requested by the HPRA.

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.

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 issue results in a 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 assessed not to have impacted upon the finished product, where finished product specifications have been met and where the requirements of EU GMP Guidelines Annex 16 (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.

Non-adherence to registered storage conditions

Any temperature excursion 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 (e.g. cracking of ampoules by freezing, which may then lead to contamination issues). Precipitation or increases in impurities may also occur.

For breaches of a short duration and/or of a marginal nature, reporting is not required 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. For wholesalers, where such data are not readily available, it may be necessary to request a risk assessment from the relevant MAH.

Unauthorised product on the market/unauthorised or erroneous distribution

Unauthorised products are defined as medicinal products that are available for sale on the Irish market without the appropriate authorisation or registration and that have not been legally distributed as an EMP (or via the Cascade system for veterinary medicines).

These defects are considered reportable once the affected units have been formally entered on to an Irish wholesaler's stock management system.

Unauthorised distribution of an Irish-authorised 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 is not always reportable to the HPRA.

For example:
- 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 is not considered reportable to the HPRA, but 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 on the inventory management system, this is not considered reportable.

Erroneous distribution can also include distribution of expired stock. If this occurs at a wholesaler in Ireland, it should be reported to the HPRA within two to three days.

APPENDIX 3 HPRA CONTACTS FOR QUALITY DEFECT ISSUES

HPRA Office Contact: +353-1-676-4971

HPRA Quality Defects and Recalls **Emergency Number** (24 hours): +353-1-634-3560