

Guide for Recall of 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.

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1 SCOPE

The purpose of this guide is to provide an analysis of the legislation relating to the recall of a medicinal product from the marketplace, and to provide guidance on the roles and responsibilities of the EU/PA/VPA/PPA holder, the manufacturer and the wholesaler in the recall process.

This guide takes into account revisions in legislation; describes the European Union (EU) classification of recalls and recall notification requirements; and outlines the basic requirements expected by HPRA in relation to recalls.

The guide covers the following categories of medicinal products:

- 1 Medicinal products which are the subject of product authorisations (PAs), veterinary products authorisations (VPAs), parallel product authorisations (PPAs) and authorisations granted by the EMA (these are known as centrally authorised products) which allows the placing of the product on the Irish, and other, EU markets with the approval of the European Commission. Note that the primary responsibility for the co-ordination of recalls of centrally authorised products (including parallel-distributed centrally authorised products) rests with the European Medicines Agency (EMA), and HPRA liaises with the EMA in such work.
- 2 Medicinal products manufactured in Ireland and which are distributed in Ireland or elsewhere;
- 3 Medicinal products distributed inside and outside the EU by Irish wholesalers and exporters;
- 4 Promotional samples of medicinal products issued to healthcare professionals;
- 5 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, medicinal products supplied in accordance with the cascade system;
- 6 Investigational Medicinal Products manufactured and distributed for the purposes of performing clinical trials.

This guide does not cover the following categories of medicinal products:

- 7 Unauthorised medicinal products which may be on the Irish market and which do not comply with any of the exemptions set out in Medicinal Products (Control of Placing

on the Market) Regulations 2007, S.I 540 of 2007, or which were not distributed in accordance with Article 10 of 2001/82/EC for veterinary medicinal products;

- 8 Products regulated under the Biocidal Products Directive (98/8/EC) or Medicated Feeding Stuffs Directive (90-167-EEC).

Where the recall of a medicinal product is required, the recall is overseen by the Market Compliance Section of the HPRA. However, continued marketing of such products may, additionally, for medicinal products for human use, be the subject of enforcement action by the HPRA or, for veterinary medicinal products, by the Department of Agriculture and Food, as appropriate.

Corrective actions arising from a recall are outside the scope of this guide and are not discussed here.

2 INTRODUCTION

2.1 Definitions and general information

A batch or product recall may be defined as:

The retrieval from the marketplace of a batch or batches of any medicinal product, whether for human or veterinary use, which is / are the subject of a quality defect, another non-compliance with the marketing authorisation, or a safety or efficacy issue. Quality related issues, which can lead to a batch or product recall, are known as quality defects.

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.

It should be noted that once a batch of a medicinal product has been Qualified Person (QP) released for marketing, has left the control of the manufacturing facility specified in Annex 1 of Schedule 2 of the manufacturer's licence, and has been made available for sale on the stock management system of the pre-wholesaler/primary wholesaler the batch is considered to have been placed onto the market. Any retrieval (for quality defect, non-compliance, safety or efficacy reasons) of product after it has been made available for sale on the pre-wholesaler's/primary wholesaler's stock management system is considered to be a batch/product recall.

There are cases where returns from a wholesaler or company subsidiary/sister company will not be classified as recalls. For example, product being returned for commercial reasons, or

due to ordering or shipping errors, or for logistical reasons will not be classified as recalls. Also, returns provided for under paragraph 5.65 of Chapter 5 of the EC Guide to GMP are not classified as recalls by HPRA.

It should also be noted that not all reports of Quality Defects result in recall actions. As part of a quality defect investigation, a company may wish to retrieve a pack of a product to assist in their quality defect investigation. For example, a company may request their primary wholesaler to send them back a pack for inspection or analysis. Such returns would not be considered recalls. However, should the investigation conclude that a recall is necessary, future returns/retrievals will be classified as recalls.

Reports of quality defects may be received by the Health Products Regulatory Authority (HPRA) from a number of sources. Quality defects are classified according to their potential threat to patient or animal well-being and public health in general. All reports of quality defects received by HPRA, and quality defects identified by HPRA staff, are investigated, and while such investigations may result in HPRA requesting the Marketing Authorisation Holder, manufacturer or wholesaler to recall the batch / product, it should be noted that this is necessary only in the minority of cases.

Recalls should be performed promptly and should result in the effective removal of the batch or product in question from the marketplace to the extent agreed with the competent authority. The extent of a recall may be to wholesale, retail or patient/user level. The purpose of this note is to provide guidance for industry on matters relating to product recalls.

All proposed recalls of medicinal product from the Republic of Ireland marketplace are required to be notified to the Market Compliance Section of HPRA in advance of the recall occurring, so that the terms of the recall can be agreed, and the implications for other products, for the supply chain, and for patients / users can be considered and evaluated. Contact details for the Market Compliance Section of the HPRA are available at www.hpra.ie. In cases where a batch or product was manufactured and / or released by a QP in the Republic of Ireland, and is being recalled in another marketplace (i.e. not in the Republic of Ireland), the Market Compliance Section must also be promptly informed of such recall actions by the QP or by the manufacturer.

Where a Quality Defects occurs at an Irish based manufacturing facility, marketing authorisation holder company or wholesaling premises, the Compliance Section considers the requirement for a for-cause inspection to be performed at the facility where the defect occurred. The requirement for such an inspection is decided on a case-by-case basis using a risk based approach. Where a for-cause inspection is not warranted, the Quality Defect issue, in particular the investigation carried out by the company and the corrective actions implemented to prevent a recurrence of the defect, will be followed up at the next routine GMP, MAH or GDP inspection.

2.2 Legal basis for requesting recalls

Appendix I sets out the legislative basis for a competent authority requesting the recall of a medicinal product, and also the legal obligations of a EU/PA/VPA/PPA holder or manufacturer, with regard to the execution and reporting of a recall.

Appendix I discusses the following:

1. Medicinal Products for Human Use

1.1. Legislation relevant to manufacturers of medicinal products for human use

1.2 Legislation relevant to Marketing Authorisation Holders of medicinal products for human use

1.3 Legislation relevant to wholesalers of medicinal products for human use

2. Medicinal Products for Veterinary Use

2.1 Legislation relevant to VPA holders and manufacturers of Veterinary Medicinal Products

2.2 Legislation specifically relevant to manufacturers of Veterinary Medicinal Products

2.3 Legislation relevant to distributors of veterinary medicinal products

2.3 Distribution of medicinal products

The distribution of medicinal products, for human or veterinary use, can follow a complex route as illustrated in Figure 1.

While the legislation refers to the 'wholesaler' as a general term, it is useful for the purposes of clarity to differentiate between primary and secondary wholesalers. A primary wholesaler is considered to be the wholesaler who first places the batch of the medicinal product on the Irish market on behalf of the Marketing Authorisation Holder. This includes all wholesalers who first receive a medicinal product for distribution in Ireland from abroad, and who distribute the product to other Irish wholesalers, directly to retailers, or to other persons entitled to receive the medicinal product. A secondary wholesaler is considered to be any wholesaler who distributes a batch of medicinal product received from another wholesaler in the Republic of Ireland.

A medicinal product may be distributed from a manufacturer to a primary wholesaler. The primary wholesaler in turn may supply directly to hospital or retail pharmacies, other retail outlets, dentists or doctors, veterinary clinics, veterinary surgeons or licensed merchants.

Alternatively, the primary wholesaler may supply a number of other secondary wholesalers who subsequently supply pharmacies and veterinary clinics etc. Therefore, to ensure a prompt and effective recall, it is essential that all persons involved in the manufacture, marketing and distribution of medicinal products have in place an adequate recall procedure which ensures that, should a recall be required, there is an effective and efficient means of communication of the recall notification between all involved, and that adequate records, which ensure traceability of the product, are maintained by each party at all stages of the supply chain.

The supply of promotional samples (physicians' samples) by sales representatives of a company should also be considered in the event of a batch or product recall. These should only be distributed in a manner which ensures their complete traceability.

2.4 Reconciliation of a Recalled Batch

The determination by the EU/PA/VPA/PPA holder or manufacturer that a recall is complete can only be made by a reconciliation of quantities returned with quantities despatched. This reconciliation can only be accomplished through accurate batch recording by the EU/PA/VPA/PPA holder and /or the manufacturer, together with properly kept distribution records by both primary and secondary wholesalers.

It is incumbent upon the manufacturer of a medicinal product to maintain comprehensive batch records, as required by the conditions of the manufacturer's licence. It is also necessary that each product label and outer carton (if present) carry its batch number in a clearly legible fashion. It is helpful (especially for wholesalers and retailers) if invoices issued for products upon dispatch from the manufacturer carry the appropriate batch numbers. (Note that for medicinal products for human use, it is not currently a legal or regulatory requirement for batch numbers to be recorded in transactions between wholesalers and retailers, and between retailers and patients/users of a medicinal product. However, the recording of batch numbers on invoices generated by wholesalers of veterinary medicinal products for product dispatch orders is a specific requirement for veterinary medicines under the Animal Remedies Regulations, 2007(SI No. 786 of 2007). See Appendix I, Section 2.3 'Legislation Relevant to Wholesalers of Veterinary Medicines', for details.)

The decision by the EU/PA/VPA/PPA holder or manufacturer that a recall is complete is communicated to the HPRA in their recall report. If HPRA accepts that the recall has been completed to an acceptable level, then the recall is closed out in HPRA's files. If not, this is communicated to the company which will be instructed to carry out additional recall actions.

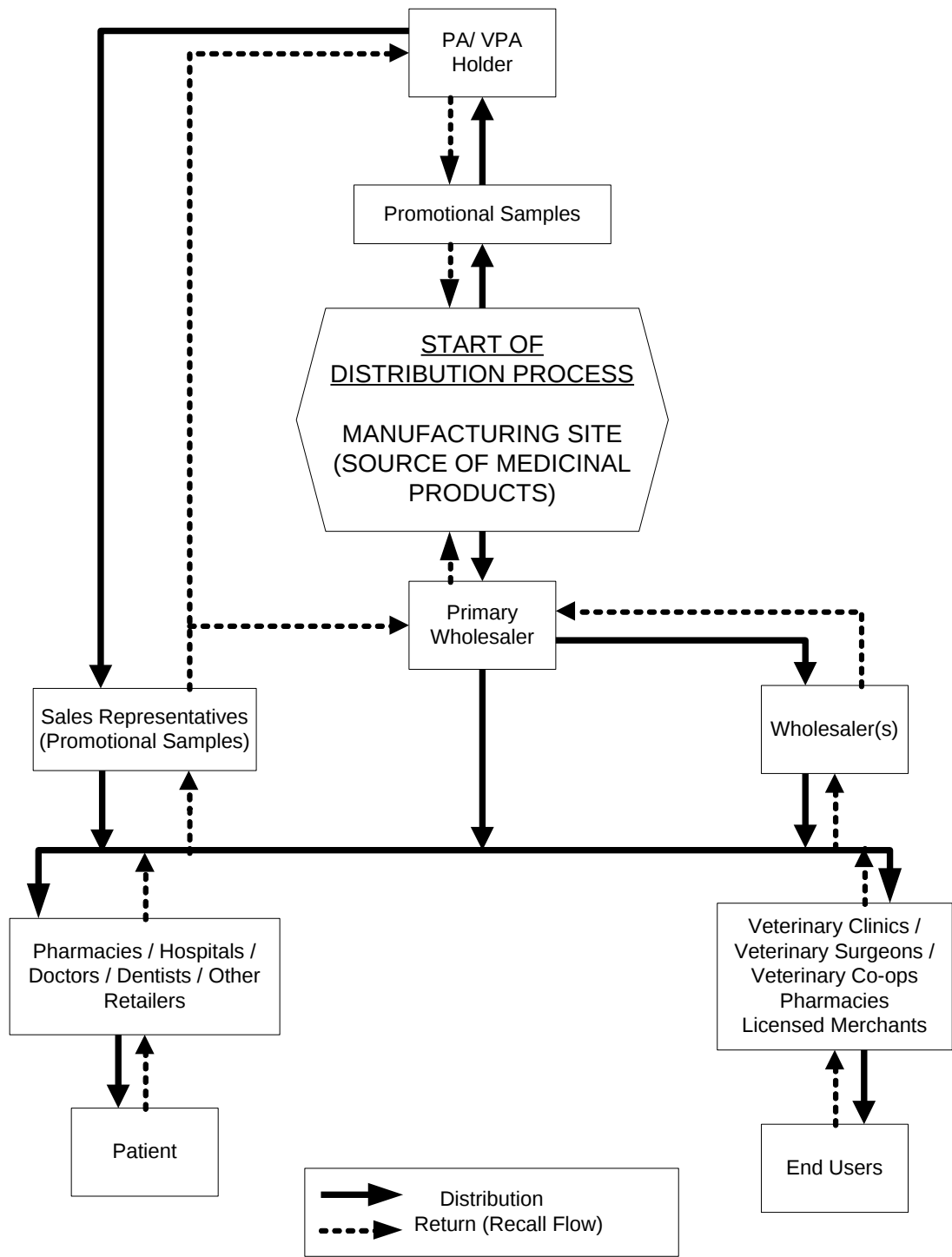


Figure 1 Distribution and Recall Flow of a Medicinal Product

3 INFORMATION ON RECALL CLASSIFICATIONS & RECALL NOTIFICATION MECHANISMS (AND CAUTION IN USE NOTIFICATIONS)

3.1 Introduction

It has proven beneficial to differentiate between serious and less serious issues which may lead to recalls. In this regard, three classes of recalls have been agreed at an EU level, classes I, II and III, the details of which are presented below.

Once a situation has arisen where it is agreed between the EU/PA/VPA/PPA Holder/Manufacturer or Wholesaler and the HPRA that a recall is required, the classification determined for the particular recall will help to determine the extent of the recall and the method by which the Recall Notification is issued. The classifications below are based on the recall classifications detailed in the 'Compilation of Community Procedures on Administrative Collaboration and Harmonisation of Inspections – Revised Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects'.

As noted above, the purpose of classifying recalls is to assist in the determination of the method and extent of the recall, and the timing of the notification, as summarised in Table 1.0 below. Sample recall notification letters are presented in Appendices V and VI.

3.1.1 Class I Recalls

These are recalls which result from quality defects of medicinal products which are potentially life threatening or could cause serious risk to health.

Examples of such quality defects:

- (i) Wrong product (label and contents are different products).
- (ii) Correct product but wrong strength, with serious medical consequences.
- (iii) Microbial contamination of sterile injectable or ophthalmic product.
- (iv) Chemical contamination with serious medical consequences.
- (v) Mix up of products ('rogues') within a pack. For example, two different blister strips within one outer carton, or, two different tablets within the one blister strip.
- (vi) Wrong active ingredient in a multi-component product with serious medical consequences.
- (vii) Serious adverse reactions which are batch or product related (most likely to be first notified to the Pharmacovigilance Section in an Urgent Safety Report).

(viii) Method and extent of recall to be considered for Class I Recalls:

- 1 Recall of the product/batch(es) to patient or user level may be necessary. If so, this can be done via announcements by the EU/PA/VPA/PPA holder or HPRA on the radio and television and/or by newspaper notifications.
- 2 Medical practitioners, pharmacists, other retailers and wholesalers should be contacted by the EU/PA/VPA/PPA holder or designee within 24 hours, where possible, notifying of the recall action and providing the required instructions. If initial communication is by a source other than by letter, there should be a follow-up letter issued to the above persons to confirm this notification.
- 3 Direct uplifting of stock, rather than allowing the return of the affected product via wholesalers, is the method of choice for retrieval of product in the case of Class I recalls.

Notification Period: within 24 hours from the time the HPRA and the Company agree on the recall action to the issue of the recall notification.

3.1.2 Class II Recalls

These are recalls due to quality defects which could cause illness or mistreatment but are not Class I.

Examples of such quality defects are:

- (i) Mislabelling - wrong or missing text or figures.
- (ii) Missing or incorrect information - leaflets or inserts.
- (iii) Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences.
- (iv) Chemical/physical contamination (significant impurities, cross-contamination, particulates).
- (v) Mix up of products ('rogues'). For example, a case of product A contains one or more packs of product B.).
- (vi) Non-compliance with specification (e.g. assay, stability, fill/weight).
- (vii) Insecure closure with serious medical consequences (e.g. cytotoxics, child-resistant containers, potent product).

Method and extent of recall to be considered for Class II Recalls:

In certain cases, telephone or telefax contact by the EU/PA/VPA/PPA holder with certain groups may be necessary. All target groups should receive a recall letter from the EU/PA/VPA/PPA holder or his/her agent. In general, such recalls should be carried out to wholesaler, retail pharmacy, hospital pharmacy, dispensing doctor, veterinarian, veterinary co-op, licensed merchant or retail grocer level as appropriate.

Notification Period: within 72 hours from the time the HPRA and the Company agree on the recall action to the issue of the recall notification.

3.1.3 Class III Recalls

These are recalls due to quality defects which are not likely to pose a significant hazard to health but where a recall has been initiated for other reasons.

Examples of such quality defects are:

- (i) Faulty packaging – for example, wrong or missing batch number or expiry date.
- (ii) Faulty closure.
- (iii) Contamination, for example, microbial spoilage, dirt or detritus, particulate matter.

Method and extent of recall to be considered for Class III Recalls:

Class III Recalls can be notified by letter to appropriate target groups by the EU/PA/VPA/PPA holder. Such recalls may be carried out to wholesale, retail, hospital and/or dispensing doctor level. In most cases however, a recall to wholesaler level may be sufficient.

Notification Period: within 5 days from the time the HPRA and the Company agree on the recall action to the issue of the recall notification.

3.1.4 Caution-In-Use Notifications (CIUN)

The nature of the product quality defect may be such that a product recall may not be considered necessary or appropriate. However, consideration should be given to the need to alert healthcare professionals who may prescribe use of, or who may distribute, dispense or administer the product, bringing to their attention details of the product defect. The issuing of a CIUN may be appropriate in this case. (See Appendix VII for a sample format of a CIUN letter).

Caution in Use notifications may be published in trade journals.

Notification Period: within 5 days from the time the HPRA and the Company agree on the CIU action to the issue of the CIU notification.

Table 1.0 Notification for recall classes and caution in use notifications *

Recall Classification	Class I	Class II	Class III	Caution in Use Notification
Notification Period**	Within 24hrs	Within 72hrs	Within 5 days	Within 5 days
Method of Notification	Phone & fax, Radio/TV (if necessary), press announcements followed by letter	Letter/Fax if necessary, followed by phone (if necessary)	Letter/Fax if necessary,	Letter
Extent of Notification	Wholesalers, pharmacies, other retailers, medical practitioners and patients,	Wholesalers, pharmacies, other retailers possibly medical practitioners	Wholesalers, possibly pharmacies and other retailers	Pharmacies, possibly medical practitioners possibly wholesalers.
Method of Retrieval of recalled stock	Direct uplift of stock	Via wholesaler	Via wholesaler	Not applicable

* Note The above are guidelines only and each recall action, the method and extent of notification and the timeline for same, shall be decided on a case-by-case basis.

** Note The Notification Periods shown in this table relate to the time from HPRA and company reaching agreement on the action to be taken, to issuing the actual notification.

4 SPECIFIC GUIDANCE AND REQUIREMENTS IN RELATION TO RECALLS FOR:

4.1 The Marketing Authorisation Holder

- 4.1.1** In relation to product distributed on the Irish market, it is the overall responsibility of the holder of the Marketing Authorisation Holder for the product concerned, to ensure that, when required, any recall required by the HPRA is implemented fully and completed expeditiously.
- 4.1.2** It is HPRA's preference that the EU/PA/VPA/PPA holder, or their Irish affiliate / subsidiary, if appropriate, takes responsibility for co-ordinating the recall and for issuing the recall notification(s). However, responsibility for these tasks may be delegated to the manufacturer or primary wholesaler who is not the EU/PA/VPA/PPA holder but, in any event, the recall should be closely monitored by a designated person at the EU/PA/VPA/PPA holder company. Where the EU/PA/VPA/PPA holder carries out the recall, this designated person will be responsible for the overall organisation, supervision and execution of the recall.
- 4.1.3** A decision to recall a medicinal product must be made in consultation with the Market Compliance Section of the HPRA. Such consultations will address the recall classification (see section 3.0 of this Guidance Note), the extent of the recall (i.e. to wholesaler, retailer or patient / user level), the mechanism for the execution of the recall, and the timelines for carrying out and completing the recall. Finally, the person responsible for recording, monitoring and reconciling the stocks involved should be named so as to facilitate liaison between the product authorisation holder, manufacturer, wholesaler and HPRA.
- 4.1.4** In general, most recalls are initiated by means of a recall letter. It is preferred that the text of the recall letter be drafted by the EU/PA/VPA/PPA holder company. The text of the letter should be agreed by the HPRA Market Compliance Section in advance of it being sent out. Sample formats of such letters are provided in Appendices V and VI of this Guidance Note.
- 4.1.5** With regard to the issuance of the recall letter(s), these should be mailed (or faxed) to the recipients, (e.g. pharmacists, wholesalers), by one person or group – the EU/PA/VPA/PPA holder, manufacturer or primary wholesaler. With respect to recall letters intended for retailers, it is usually not appropriate to delegate the mailing (or faxing) of such recall letters to secondary wholesalers. When recall letters are to be mailed to all pharmacies, or licensed merchants in the case of veterinary medicinal products, the EU/PA/VPA/PPA holder must ensure that an accurate and up to date list of pharmacies or licensed merchants is used in the mailing. The list of pharmacies can be obtained from the Pharmaceutical Society of Ireland (PSI). (Please note that the Pharmaceutical Society of Ireland (PSI) list of pharmacies does not include all hospital pharmacies, only those which keep 'open shop' and consequently companies should

ensure that any recall to hospital pharmacies captures all affected hospitals.) The list of licensed merchants can be obtained from the Department of Agriculture and Food (Veterinary Medicines Section of the Animal Health & Welfare Division). When a recall is going to wholesale level only, the EU/PA/VPA/PPA holder or manufacturer or primary wholesaler must ensure that all wholesalers who could have received the product in question are notified. (This includes the notification of wholesalers involved in wholesaler-to-wholesaler transactions.)

4.1.6 There are cases where a more urgent means of communication is required to initiate a recall. These can include:

- telephone
- e-mail
- fax
- TV
- radio
- press notices

Such actions are decided on a case-by-case basis. The EU/PA/VPA/PPA holder should liaise closely with HPRA's Market Compliance Section when an urgent means of communication is required for a recall. Note that a follow-up mailed recall letter should be issued following such notifications.

4.1.7 The determination that a recall is complete can only be made by performing a reconciliation of the quantities returned in the recall with the quantities dispatched. This reconciliation can be accomplished through accurate batch recording by the manufacturer, together with properly kept distribution records by wholesalers.

4.1.8 HPRA must be kept informed of the progress of the recall action, and should receive a full report on completion of the recall from the EU/PA/VPA/PPA holder or manufacturer. The expected timeframe is within six weeks from the date of mailing of the letters. If HPRA accepts that the recall has been completed to an acceptable level, then the recall is closed out in HPRA's files. If not, this is communicated to the company who are instructed to carry out the recall notification again. Refer to Section 7.0 for the specific details to be included in the recall report.

4.2 The Manufacturer (Manufacturing in Ireland)

4.2.1 In relation to product on the Irish market, manufactured by an Irish manufacturer, the manufacturer, in conjunction with the holder of the authorisation for the product involved, should ensure that any recall required by the competent authority is implemented fully and completed expeditiously.

4.2.2 Where a potential recall situation has been identified by a manufacturer, the Qualified Person (QP) at the manufacturer is required to contact the HPRA in order to discuss

whether a recall is necessary. This is required under chapter 8 of the EC Guide to Good Manufacturing Practice.

- 4.2.3 As noted above, responsibility for carrying out the recall may be delegated to the manufacturer by the EU/PA/VPA/PPA holder. Where the manufacturer is directly responsible for carrying out the recall, the QP should play a key role in the overall organisation, supervision, execution and completion of the recall.
- 4.2.4 Where the communication of the recall (be it by mail or otherwise) has been delegated to the manufacturer by the EU/PA/VPA/PPA holder, points noted in sections 4.1.4 - 4.1.6 above, in relation to recall communications, also apply to the manufacturer.
- 4.2.5 With respect to recalls from a market other than Ireland:
- 1 Where all or part of a batch which is the subject of a recall has been manufactured in Ireland and exported to another EU/EEA Member State or third country, the QP who released the batch has a responsibility to follow up with the marketing authorisation holder and/or wholesaler in the countries concerned in order to notify these parties of the recall issue. In doing so, the QP must ensure (subject to 4.2.7 below) that the batch is expeditiously recalled and that all recalled units are either returned or disposed of in a controlled manner. The QP should inform the HPRA Market Compliance Section of these actions.
 - 2 In relation to medicinal products manufactured in Ireland and exported to another EU/EEA Member State or third country, recalls in another market should be agreed in advance with the Competent Authority of the country concerned. The QP should play a role in ensuring that such notifications are made in the country concerned.
- 4.2.6 Where a bulk batch, which is the subject of a recall, has been sent to a site or sites inside or outside of Ireland for final packaging, the QP has a responsibility to inform all of those sites, in addition to HPRA's Market Compliance Section, of the recall.
- 4.2.7 Where a batch has been imported into Ireland from outside the EU/European Economic Area (EEA) and is released onto the Irish market by the QP of an Irish manufacturer, the overall responsibility for the release of the batch in the EU/EEA rests with the QP of the Irish manufacturer. The same QP is also responsible for co-ordinating the recall of all portions of the batch in the EU/EEA. (Refer to Annex 16 of the EC Guide to Good Manufacturing Practice.)
- 4.2.8 Where a decision is taken in another EU/EEA Member State or third country market to recall a batch which has been manufactured or released in Ireland, the QP should

immediately inform the HPRA of the recall so that HPRA can assess the events which led to the recall and the corrective actions put in place as a result.

- 4.2.9 In all cases the HPRA must be kept informed of the progress of the execution of the recall and the manufacturer must supply a final report, on completion of the recall, to the HPRA. If HPRA accepts that the recall has been completed to an acceptable level, then the recall is closed out in HPRA's files. If not, this is communicated to the company which is instructed to carry out the recall notification again. Refer to Section 7.0 for specific details to be included in the recall report.

4.3 The Wholesaler

- 4.3.1 In the case of the wholesale of medicinal products for human use, there may be practical difficulties in maintaining full batch traceability, especially in transactions with retailers. For transactions between wholesalers, wholesaler records should ensure the traceability of the origin and destination of products, for example, by use of batch numbers, so that all the suppliers of, or those supplied with, a medicinal product can be identified.
- 4.3.2 The HPRA recommends that traceability by batch number be established by all wholesalers for all transactions, where feasible. HPRA encourages all wholesalers to introduce such systems with a view to providing a satisfactory and efficient outcome in the event of a recall.
- 4.3.3 Where a medicinal product which is the subject of a recall has been distributed outside of Ireland by a wholesaler, the Responsible Person of the wholesaler should immediately notify the Market Compliance Section of the HPRA so that the HPRA can liaise with other Competent Authorities as required. The wholesaler should also formally notify customers outside Ireland and should ensure that the product is recalled effectively.

4.3.4 The Primary Wholesaler

- 1 While overall responsibility for any recall usually rests with the holder of a marketing authorisation and/or the manufacturer, the route through which a recall is channelled is generally through the primary wholesaler, if one exists. The role of the primary wholesaler is usually to quarantine stocks of the batch(es) at hand, and to receive and quarantine returns received back in the recall, where applicable, and to assist the EU/PA/VPA/PPA holder or manufacturer in the execution of the recall.
- 2 This means that all stock returned in a recall normally goes to the primary wholesaler. The dispositioning of such stock is usually agreed on a case-by-case basis with the Market Compliance Section of the HPRA. Given the central role

played by the primary wholesaler in the distribution and recall of medicinal products, the task of tracking the progress of the recall is often delegated to the primary wholesaler, who will often generate stock reconciliation data for the recall.

- 3 The Responsible Person at the primary wholesaler should monitor the progress of the recall in order to ensure the speedy recovery of the recalled product and reconciliation with the original batch quantities.
- 4 In order to meet these responsibilities relating to the recall of a distributed product, the primary wholesaler, acting as an agent for a manufacturer or a EU/PA/VPA/PPA holder, should maintain records of the batch numbers of each product received, and of the subsequent distribution of those batches of product. Note: this is a mandatory requirement for wholesalers of veterinary medicinal products for all products distributed, and for wholesalers of medicinal products for human use when supplying products to other wholesalers.
- 5 In cases where the Quality Defect Occurs at a primary wholesaling premises, the primary wholesaler will have a greater role in discussions concerning the requirement for market action and in the execution of the recall.
 - 5.1 Where a potential recall situation is the result of the occurrence of a Quality Defect at a wholesaling facility, the Responsible Person (RP) at that facility is required to contact the HPRA in order to discuss whether a recall is necessary. The RP should also inform the relevant MAH(s) for the product(s) affected.
 - 5.2 If a recall action is required, the responsibility for co-ordination of the recall is decided by the primary wholesaler and the MAH(s). Where the primary wholesaler is directly responsible for carrying out the recall, the RP should play a key role in the overall organisation, supervision, execution and completion of the recall.
 - 5.3 Where the communication of the recall (be it by mail or otherwise) is required of the primary wholesaler, points noted in sections 4.1.4 - 4.1.6 above, in relation to recall communications, also apply to the primary wholesaler.
 - 5.4 HPRA must be kept informed of the progress of the execution of the recall and the primary wholesaler must provide a final report, on completion of the recall, to the HPRA. If HPRA accepts that the recall has been completed to an acceptable level, then the recall is closed out in HPRA's files. If not, this is communicated to the primary wholesaler who is instructed to carry out the recall notification again. Refer to Section 7.0 for specific details to be included in the recall report.

4.3.5 The Secondary Wholesaler

- 1 The role of the secondary wholesaler in a recall is generally restricted to:
 - quarantining stock of the batch(es) at hand,
 - ensuring that wholesale customers supplied directly by that wholesaler are notified of the recall
 - receiving and quarantining (recalled) stock from its customers (other wholesalers, retailers or other persons entitled to receive medicinal products),
 - transporting the quarantined stock back to the primary wholesaler.
- 2 The secondary wholesaler should follow the instructions provided in the recall notification supplied either by the EU/PA/VPA/PPA holder, manufacturer, primary wholesaler or the HPRA.
- 3 It is the responsibility of the Responsible Person at the secondary wholesale company to ensure that the above requirements have been met.
- 4 In cases where the Quality Defect Occurs at a wholesaling premises, the wholesaler will have a greater role in discussions concerning the requirement for market action and in the execution of the recall.
 - 4.1 Where a potential recall situation is the result of the occurrence of a Quality Defect at a secondary wholesaling facility, the Responsible Person (RP) at that facility is required to contact the HPRA in order to discuss whether a recall is necessary. The RP should also inform the MAH(s) for the product(s) affected.
 - 4.2 If a recall action is required, the responsibility for co-ordination of the recall is decided by the secondary wholesaler and the MAH(s). Where the secondary wholesaler is directly responsible for carrying out the recall, the RP should play a key role in the overall organisation, supervision, execution and completion of the recall.
 - 4.3 Where the communication of the recall (be it by mail or otherwise) is required of the secondary wholesaler, points noted in sections 4.1.4 - 4.1.6 above, in relation to recall communications, also apply to the wholesaler.
 - 4.4 HPRA must be kept informed of the progress of the execution of the recall and the secondary wholesaler must provide a final report, on completion of the recall, to the HPRA. If HPRA accepts that the recall has been completed to an acceptable level, then the recall is closed out in HPRA's files. If not, this is

communicated to the secondary wholesaler who is instructed to carry out the recall notification again. Refer to Section 7.0 for specific details to be included in the recall report.

4.4 Unauthorised Medicinal Products

4.4.1 Exempt medicinal products for human use may be supplied by manufacturers or wholesalers to the order of a registered doctor or a registered dentist for use by his/her individual patients under his/her direct personal responsibility, as per Paragraph 2 of Schedule 1 to the Medicinal Products (Control of Placing on the Market) Regulations 2007. In the case of unauthorised veterinary medicinal products, these may only be supplied in accordance with the cascade system set out in Article 10 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. Such unauthorised products present particular issues, as it can be difficult to determine if these products are on the Irish market because they are frequently distributed via unconventional routes.

4.4.2 Manufacturers and wholesalers requested to supply such medicinal products on an unauthorised basis, should obtain confirmation (written or otherwise) that the supply is in response to a *bona fide* unsolicited order. It is not a requirement to request details of patient names or patient ID numbers, nor is it a requirement for the practitioner to sign the confirmation. Please refer to the Health Products Regulatory Authority 'Guidance Note for the Notification for Exempt Medicinal Products' for further information in relation to this.

Manufacturers and wholesalers should maintain batch traceability of medicinal products they supply on an unauthorised/exempt basis. It is strongly recommended that Irish wholesalers put in place a technical agreement with each of their supplier(s) of any unauthorised medicinal product(s). Such an agreement should require the supplier of the product to inform the Irish wholesaler in the event of the recall of any relevant batch of the product. The wholesaler should then contact the HPRA if they are in receipt of such a notification from the supplier.

4.5 Parallel Imported Products (PPAs)

4.5.1 Parallel importation is the importation from an EU Member State or a country within the European Economic Area (EEA) of a medicinal product which is already authorised on the Irish market, by an importer who is someone other than the importer appointed by the marketing authorisation holder of the product for the Irish market. A Parallel Product Authorisation (PPA) number is assigned by HPRA to the product in this case.

4.5.2 In the event of a recall of a medicinal product, it is imperative that formal agreements are in place between the parallel importer (i.e. the PPA holder company) and the

wholesaler in the other Member State, or other country within the EEA, from which the parallel importer has purchased the product, so that the parallel importer is notified of any potential recall of the product in another Member State or EEA country.

5 MINIMUM CONTENTS OF THE RECALL PROCEDURE FOR MARKETING AUTHORISATION HOLDERS AND MANUFACTURERS

5.1 Scope and Content of the Recall Procedure

EU directives and National legislation require that EU/PA/VPA/PPA holders, and manufacturers and wholesalers of human and veterinary medicinal products, have established procedures in place to enable the recall of a defective product from sale or supply, if deemed necessary. (Refer to Appendix I). The European Community Guide to Good Manufacturing Practice (GMP) – Volume IV of the Rules Governing Medicinal Products - is applicable to the manufacture of medicinal products for both human and veterinary use. The Guide stipulates the establishment of written procedures which will be implemented as the need for a recall arises. EU Guidelines on Good Distribution Practice (GDP) of Medicinal Products for Human Use (94/C 63/03) also stipulates the establishment of written recall procedures by wholesalers of medicinal products for human use.

For a EU/PA/VPA/PPA holder or manufacturer, the scope and content of the recall procedure will vary depending on the originator of the procedure i.e. whether the originator is the EU/PA/VPA/PPA holder or the manufacturer. However, there are some basic points that should be contained in the recall procedure, regardless of who the originator is and regardless of the complexity of its business. The recall procedure should contain, as a minimum, the following information / points.

- 5.1.1** 24 hour contact names, phone, including mobile phone, and fax numbers (if available) of at least three persons. Note that such contact details could be in the form of another controlled document which is referenced in the Recall procedure. The Qualified Person (at the manufacturer) should be one of the contact persons listed in the recall procedure of the manufacturer. Due account should be taken of weekend and holiday cover as well as sick leave, etc. (It is usual for a minimum of three contacts to be named in order to allow for this. However, in the case of smaller organisations, two contact names may be acceptable.)
- 5.1.2** Reference should also be made to HPRA contact details. The names of current HPRA quality defect and recall contacts, along with office and mobile telephone numbers, are available in the Medicines section of HPRA's website (www.hpra.ie).
- 5.1.3** The procedure should state that all recalls, regardless of whether the product is distributed in Ireland or abroad, should be notified to HPRA's Market Compliance

Section prior to any recall action being taken. This notification can initially be via telephone, but should always be followed with a letter / fax e-mail or an on-line notification. For serious quality defects, it is preferable that initial contact is made via telephone and then followed up with a formal written notification.

5.1.4 The procedure should state that potential recalls, serious quality defects, defects which could result in an abnormal restriction of supply, and defects or complaints which could potentially lead to a recall, should be brought to the attention of HPRA's Market Compliance Section at an early time-point. (Note: It is stressed that notification of these issues to HPRA may not necessarily result in a batch or product recall). The procedure should list the information which should be provided to HPRA during such a notification. The information to be provided is as follows:

- Product name
- Active Substance Name
- Product strength
- Pharmaceutical form (e.g. tablets, solution for injection, powder for solution for infusion, etc.)
- Description of package (e.g. 28 capsules in a polyethylene tub, two blisters each of 30 tablets in a carton, etc.)
- Batch numbers and expiry date information for each batch
- Finished product manufacturer's name and address
- EU/PA/VPA/PPA number(s)
- Name and address of EU/PA/VPA/PPA holder
- Name of the primary wholesaler in Ireland
- Complete description of the quality defect / reason for the proposed recall
- Reporter's name, organisation and address, telephone / telefax numbers and e-mail address.
- Date reported to HPRA

5.1.5 The procedure should state that, once initial contact has been made with the HPRA, the actions to be taken shall be discussed and agreed upon. This will include the

classification, extent and method of notification of any recall required. (Guidance on the classification, extent and method of notification of recalls is given in section 3.0 of this Guidance Note.)

- 5.1.6 The procedure should state that all recall notifications being issued by the company should be discussed, reviewed and approved by HPRA's Market Compliance Section in advance of their issuance. This applies to all written communications to healthcare professionals and wholesalers on the subject of batch or product recalls, or quality related matters, and also to written communications providing cautionary advice to physicians, pharmacists and other healthcare professionals on a product or batch quality defect (Caution-in-Use Notifications (CIUNs)).
- 5.1.7 The procedure should give guidance on how to write and structure recall notifications to wholesalers, pharmacists and other groups. All recall notifications being issued by a company to wholesalers, pharmacists and other groups should:
- 1 Be short (preferably no more than one A4 page in length), informative, (providing all the necessary information to the reader), and free of unnecessary information and promotional statements.
 - 2 Contain simple, unambiguous language. The overall subject matter (for example, a batch recall of a particular product) should be prominently displayed at the top of the letter in bold, centred text. Three examples of letters are presented in Appendices V, VI and VII of this Guidance Note and they show the formats and text elements that are generally requested by HPRA for such communications. The Market Compliance Section is available at all times to provide assistance and advice on the text and format of such communications.
 - 3 It should be noted that all agreed, written communications concerning product or batch recalls, and CIUN notifications, should carry a statement to the effect that the actions being undertaken have been agreed with the Health Products Regulatory Authority. This provides assurance to the reader that the instructions or advice being provided have been agreed with the HPRA.
- 5.1.8 The procedure should address situations in which there is a need to issue press releases in order to caution the public in the use of a product known to be defective but where a product recall is either not feasible or is not considered necessary. The above requirements still apply, i.e. all such notifications should be discussed and agreed with the Market Compliance Section of the HPRA in advance of their issuance, and consideration shall be given to points (1) to (3) in section 5.1.7 above when drafting the notification.

5.1.9 For manufacturers, the recall procedure should describe, or include a reference to, the system which identifies where the product or the specific batches of the product have been distributed.

5.1.10 The procedure should require the submission of a full report of the recall to the HPRA Market Compliance Section upon completion of the recall. Guidance on the preparation of this recall report is given in Section 7.0.

5.2 Challenging the Recall Procedure

5.2.1 The recall procedure should be challenged to ensure that it is effective - this may involve verifying the accuracy of contact names and numbers, and challenging the company's product traceability procedures and batch reconciliation procedures. Ideally, and where possible, the EU/PA/VPA/PPA Holder/Manufacturer should include the wholesaler in this challenge, or should obtain confirmation from the wholesaler that its recall procedure is effective. It is recommended that the recall procedure is challenged on an annual basis, unless the EU/PA/VPA/PPA Holder or Manufacturer has executed a recall within that timeframe.

5.3 Copying the Recall Procedure to HPRA

5.3.1 A copy of the current recall procedure for each Irish marketing authorisation holder and manufacturer should be provided to HPRA's Market Compliance Administration section. This provides HPRA with a ready means of contacting the appropriate persons (both within and outside office hours) in the event of a potential recall. (Please note that copies of recall procedures should not be sent to the product licensing departments of HPRA).

6 MINIMUM CONTENT OF THE RECALL PROCEDURE FOR WHOLESALERS

6.1 Wholesaler

For a wholesaler, the scope and content of the recall procedure will include the following issues, as in section 5.0 above:

6.1.1 24-hour contact names, phone, including mobile phone, and fax numbers (if available) of at least three persons. The Responsible Person (at the wholesaler) should be one of these contacts. Due account should be taken of weekend and holiday cover as well as sick leave, etc. (It is usual for a minimum of three contacts to be named in order to allow for this, however in the case of smaller organisations, two contact names may be acceptable.))

- 6.1.2 Reference should also be made to HPRA contact details. The names of current HPRA quality defect and recall contacts, along with office and mobile telephone numbers, are available in the Medicines section of the HPRA's website (www.hpra.ie).

In addition to this, the following points, with regard to the content of the recall procedure for a wholesaler, should be noted:

- 6.1.3 The wholesaler's recall procedure should include a reference to the method for contacting and informing the EU/PA/VPA/PPA holder of a quality defect in a product discovered by the wholesaler. For primary wholesalers, EU/PA/VPA/PPA holder contact names, addresses and phone numbers should be maintained on file for this purpose.
- 6.1.4 The procedure should state that the recall should be carried out either on foot of a notification from the EU/PA/VPA/PPA holder, or from the HPRA.
- 6.1.5 The procedure should state that the recall shall be initiated immediately on receipt of a recall notification. The timelines referenced in Section 3 and Table 1.0 may be used as a guide. As stated previously, each recall is considered on a case-by-case basis by the HPRA.
- 6.1.6 The recall procedure should describe, or include a reference to, the system which identifies where the product or specific batches of the product have been distributed.
- 6.1.7 The procedure shall describe the placing of recalled goods in a secure quarantined area. (It would not generally be expected that the wholesaler should have a permanently designated secure area for recalled goods, as this can vary largely depending on the product which may be recalled).
- 6.1.8 The procedure should describe the preparation of a report on the reconciliation of the recalled product / batch(es). This report should be forwarded to the EU/PA/VPA/PPA holder when complete. Refer to Section 7.0 below for guidance on the preparation of this report.
- 6.1.9 The procedure should also include a description of the system for the maintenance of a Recall Log.

In addition, to account for cases where the quality defect occurs at a wholesaling premise, the recall procedure should include the following:

- 6.1.10 The procedure should state that all recalls, regardless of whether the product is distributed in Ireland or abroad, the RP of the wholesaling facility where the quality defect occurs should notify HPRA's Market Compliance Section prior to any recall action being taken. This notification can initially be via telephone, but should always

be followed with a letter / fax e-mail or an on-line notification. For serious quality defects, it is preferable that initial contact is made via telephone and then followed up with a formal written notification.

6.1.11 The procedure should state that potential recalls, serious quality defects, defects which could result in an abnormal restriction of supply, and defects or complaints which could potentially lead to a recall, should be brought to the attention of HPRA's Market Compliance Section at an early time-point. (Note: It is stressed that notification of these issues to HPRA may not necessarily result in a batch or product recall). The procedure should list the information which should be provided to HPRA during such a notification. The information to be provided is as follows:

- Product name
- Active Substance Name
- Product strength
- Pharmaceutical form (e.g. tablets, solution for injection, powder for solution for infusion, etc.)
- Description of package (e.g. 28 capsules in a polyethylene tub, two blisters each of 30 tablets in a carton, etc.)
- Batch numbers and expiry date information for each batch
- Finished product manufacturer's name and address
- EU/PA/VPA/PPA number(s)
- Name and address of EU/PA/VPA/PPA holder
- Name of the primary wholesaler in Ireland (if applicable)
- Complete description of the quality defect / reason for the proposed recall
- Reporter's name, organisation and address, telephone / telefax numbers and e-mail address.
- Date reported to HPRA

6.1.12 The procedure should state that, once initial contact has been made with the HPRA and the EU/PA/VPA/PPA Holder(s) of the concerned product(s), the actions to be taken shall be discussed and agreed upon. This will include the classification, extent

and method of notification of any recall required. (Guidance on the classification, extent and method of notification of recalls is given in section 3.0 of this Guidance Note.)

6.1.13 The procedure should state that all recall notifications being issued by the wholesaler should be discussed, reviewed and approved by HPRA's Market Compliance Section in advance of their issuance. This applies to all written communications to healthcare professionals and other wholesalers on the subject of batch or product recalls, or quality related matters, and also to written communications providing cautionary advice to physicians, pharmacists and other healthcare professionals on a product or batch quality defect (Caution-in-Use Notifications (CIUNs)).

6.1.14 The procedure should give guidance on how to write and structure recall notifications to other wholesalers, pharmacists and other groups. All recall notifications being issued by a wholesaler to other wholesalers, pharmacists and other groups should:

- 1** Be short (preferably no more than one A4 page in length), informative, (providing all the necessary information to the reader), and free of unnecessary information and promotional statements.
- 2** Contain simple, unambiguous language. The overall subject matter (for example, a batch recall of a particular product) should be prominently displayed at the top of the letter in bold, centred text. Three examples of letters are presented in Appendices V, VI and VII of this Guidance Note and they show the formats and text elements that are generally requested by HPRA for such communications. The Market Compliance Section is available at all times to provide assistance and advice on the text and format of such communications.
- 3** It should be noted that all agreed, written communications concerning product or batch recalls, and CIUN notifications, should carry a statement to the effect that the actions being undertaken have been agreed with the Health Products Regulatory Authority. This provides assurance to the reader that the instructions or advice being provided have been agreed with the HPRA.

6.1.15 The procedure should address situations in which there is a need to issue press releases in order to caution the public in the use of a product known to be defective but where a product recall is either not feasible or is not considered necessary. The above requirements still apply, i.e. all such notifications should be discussed and agreed with the Market Compliance Section of the HPRA in advance of their issuance, and consideration shall be given to points (1) to (3) in section 6.1.14 above when drafting the notification.

- 6.1.16 The procedure should require the submission of a full report of the recall to the HPRA Market Compliance Section upon completion of the recall. Guidance on the preparation of this recall report is given in Section 7.0.

6.2 Challenging the Recall Procedure

- 6.2.1 The recall procedure should be challenged to ensure that it is effective - this may involve verifying the accuracy of contact names and numbers, and challenging the company's product traceability procedures and batch reconciliation procedures. It is recommended that the recall procedure is challenged on an annual basis, unless the wholesaler has executed a recall within that timeframe.

6.3 Copying the Recall Procedure to HPRA

- 6.3.1 A copy of the current recall procedure for each Irish wholesaler should be provided to HPRA's Market Compliance Administration section.

7 REQUIREMENTS RELATING TO RECALL REPORTS

7.1 Introduction

On completion of a recall, a full report of the details of the recall, and the recall actions that were taken, must be submitted to HPRA's Market Compliance Section for review. The expected timeframe for receipt of the recall report is four to six weeks from the date of mailing of the letters.

This report must provide information on the reconciliation of stocks, and should describe the steps taken to investigate and to correct the source of the quality defect or other issue which led to the recall. If a recall report cannot be submitted within six weeks from the date of mailing of the letters, interim reports should be provided to HPRA at appropriate intervals as agreed with HPRA's Market Compliance Section.

The overall responsibility for preparing the recall report and for forwarding the report to HPRA's Market Compliance Section rests with the PA / VPA holder, *though this action may be delegated to the manufacturer by the EU/PA/VPA/PPA holder with the agreement of HPRA.*

In many cases, the primary wholesaler may prepare certain sections of the recall report, particularly the section relating to the reconciliation of stocks returned to the primary wholesaler. The primary wholesaler should forward this section of the report to the EU/PA/VPA/PPA holder for inclusion as an Appendix to the EU/PA/VPA/PPA holder's recall

report. Unless requested by the HPRA's Market Compliance Section, the primary wholesaler should not forward their recall report to the Market Compliance Section separately to, and independently from, the PA/VPA holder's report. While secondary wholesalers should not be responsible for preparing the reconciliation section of the recall report, they are required to forward information to the primary wholesaler concerning the stock recovered by them and being returned to the primary distributor.

7.2 Marketing Authorisation Holder and Manufacturer Recall Reports

7.2.1 The marketing authorisation holder's / manufacturer's recall report should typically contain four sections, titled:

- An Executive Summary
- Details of the Recall
- Results of the Recall
- A brief Tabulated Chronological Account of the events which led to the recall

These are detailed below;

- 1 The **Executive Summary** should provide an overview of what occurred. It should be brief, approximately half a page in length, and it should describe the quality defect issue (or the issue which led to the recall) and the subsequent recall action(s) taken.
- 2 The section titled '**Details of the Recall**' should include:
 - Product name
 - Active substance name
 - Product strength
 - Pharmaceutical form (e.g. tablets, solution for injection, powder for solution for infusion, etc.)
 - Description of the packaged product (e.g. tablets in a polyethylene tub, blisters in a carton, etc.)
 - Batch number(s) being recalled and expiry date information for such batch (es)
 - EU/PA/VPA/PPA number(s)
 - Name and address of the manufacturer of the finished product which performed QP release to the marketplace

- Name and address of the primary wholesaler (if applicable)
- Reason for the recall (include a full description of the quality defect issue and the extent of such)
- Mechanism of the recall (e.g. by letter, telephone or fax, etc.)
- Extent of the recall (e.g. to primary wholesaler, wholesaler, pharmacy or patient/user level, as applicable)
- Territory of product distribution (i.e. country names)
- Total quantity of packs manufactured for the affected batch(es)
- Total quantity distributed for the affected batch(es)
- Cause of the quality defect
- Specific corrective actions arising from the investigation into the cause of the quality defect or other issue, and the timelines for the completion of each of the corrective actions identified
- Copies of the signed and dated Recall Notification letters sent out during the course of the recall.
- Date of Close Out of the recall.

3 The section titled '**Results of the Recall**' (this is sometimes called the *Reconciliation Report*), should state:

- The total quantity of packs recovered in the recall from the primary wholesaler and from other (secondary) wholesalers. Note that the number of packs recovered from the primary wholesaler and from other (secondary) wholesalers in the recall may include packs which were returned to them by retailers, hospitals and other groups.
- Note that if retailers and other persons were asked to return product directly to the primary wholesaler or manufacturer, or if a direct uplift of product from retailers and/or other persons occurred, then the quantity of packs recovered from these specific groups in the recall should be stated here also.

- The percentage of packs reconciled per batch, (i.e. number of packs received back as a percentage of the number of packs distributed per batch recalled.)
- The overall percentage of packs reconciled, (i.e. number of packs received back as a percentage of the number of packs distributed for all batches recalled.)

Note: % reconciliation is the number of packs recovered calculated as a percentage of the number of packs distributed.

4 The **Tabulated Chronological Account** of the events which led to the recall should include:

- The date the quality defect or other issue was first discovered by the EU/PA/VPA/PPA holder or manufacturer.
- The date the quality defect or other issue was reported to the HPRA.
- Dates of all subsequent key communications with HPRA.
- Date of approval by the HPRA of the actions to be undertaken to address the quality defect or other issue.
- Date of approval by HPRA of the recall notification letter(s) and / or Caution-In-Use letter.
- Date of the initiation of the recall and dates of sending out the recall notification letter. Copies of these letters should be included as an appendix to the report.
- Dates of other actions taken by the company in order to ensure that a satisfactory recall was executed.
- Date of the close out of the recall and the sending of the final recall report to HPRA. (Note that the EU/PA/VPA/PPA holder or manufacturer should consult with the Market Compliance Section in advance to determine when the recall may be considered closed.)
- Planned completion dates for outstanding corrective actions arising from the recall.

7.3 Wholesaler's Recall Report

7.3.1 The purpose of the primary wholesaler's recall report is to provide the following key information, where relevant:

- 1 the number of packs of the recalled batch(es) which were held in stock at the primary wholesaler's facility when the recall was first initiated;
- 2 the number of packs returned to the primary wholesaler from secondary wholesalers;
- 3 the number of packs returned directly to (or uplifted by) the primary wholesaler from pharmacists or other retailers/groups;
- 4 a calculation of the total number of packs of each batch received back as a percentage of the total number of packs of each batch distributed (this is the % reconciliation);
- 5 a brief chronological account of the recall events as they occurred at the primary wholesaler.

Note that if the recall action was taken as a result of an error which occurred at a primary wholesaling facility, then information on the specific corrective actions to be implemented at the primary wholesaler to address the issue, and the timelines for the completion of each of the corrective actions identified, should be provided in the primary wholesaler's recall report.

7.3.2 The primary wholesaler's recall report should typically contain 3 sections, titled:

- Details of the Recall
 - Results of the Recall
 - Tabulated Chronological Account of the events which led to the recall at the primary wholesaler
- 1 (The section titled 'Details of the Recall' should include:
 - Product Name
 - Product Strength
 - Pharmaceutical Form (e.g. tablets, solution for injection, powder for solution for infusion, etc.)
 - Description of the packaged product (e.g. tablets in a tub, blisters in a carton, etc.)
 - Batch numbers recalled and expiry date information for such batches

- EU/PA/VPA/PPA number(s)
 - Reason for the recall
 - Extent of the recall (e.g. to primary wholesaler, wholesaler, pharmacy/retail or patient/user level, as applicable)
 - Total quantity of packs received by the primary wholesaler for each of the affected batch(es)
 - Total quantity distributed to secondary wholesalers, pharmacies or other retail outlets, for the affected batch(es)
 - Cause of the quality defect
 - Specific corrective actions to be implemented by the primary wholesaler addressing the issue which led to the recall, and the timelines for the completion of each of the corrective actions identified. Note that this only applies if the recall action was taken as a result of an error that occurred at the primary wholesaler.
- 2 The section titled '**Results of the Recall**' (this is sometimes called the *Reconciliation Report*), should state the total quantity of packs recovered in the recall from the primary wholesaler's warehouse and from other (secondary) wholesalers. Note that the number of packs recovered from the primary wholesaler's warehouse and from other (secondary) wholesalers in the recall may include packs which were returned to them by retailers, hospitals and other groups.
- Note that if retailers and other persons were asked to return product directly to the primary wholesaler, or if a direct uplift of product from retailers and/or other persons was executed by the primary wholesaler, then the quantity of packs recovered from these specific groups in the recall should be stated here also.
 - The percentage of packs reconciled per batch, (i.e. number of packs received back as a percentage of the number of packs distributed by the primary wholesaler per batch recalled.)
 - The overall percentage of packs reconciled, (i.e. number of packs received back as a percentage of the number of packs distributed for all batches recalled.)
- Note: % reconciliation is the number of packs recovered calculated as a percentage of the number of packs distributed.

- 3 The section titled 'A brief Tabulated Chronological Account of the recall events as they occurred' should include:
- The date the notification of the recall was received by the primary wholesaler.
 - Dates of the quarantining of stock held by the primary wholesaler.
 - The dates within which the recalled packs were received back at the primary wholesaler from other groups (i.e. from secondary wholesalers, pharmacists or other retail outlets, as applicable), and dates these packs were quarantined.
 - Date of closing out of the recall at the primary wholesaler, and the date the primary wholesaler's recall report was sent to the EU/PA/VPA/PPA holder or manufacturer.

Note that if the recall action was taken as a result of a quality defect which occurred at a secondary wholesaling facility, a recall report as outlined above should be submitted to the HPRA by the secondary wholesaler. This report should include information on the specific corrective actions to be implemented at the secondary wholesaling facility to address the issue, and the timelines for the completion of each of the corrective actions identified.

8 FURTHER INFORMATION

For further information, contact:

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APPENDIX I LEGAL BASIS FOR REQUESTING RECALLS

The following sets out the legislative basis for the HPRA requesting the recall of a medicinal product, and also the legal obligations of a MA holder, manufacturer or wholesaler, with regard to the execution and reporting of a recall.

Please note that wherever the term PA or MA holder is used it should be taken to include herbal and homeopathic registration numbers and holders.

This section is structured as follows:

1 Medicinal Products for Human Use

- 1.1. Legislation relevant to manufacturers of medicinal products for human use
- 1.2 Legislation relevant to Marketing Authorisation Holders of medicinal products for human use
- 1.3 Legislation relevant to wholesalers of medicinal products for human use

2. Medicinal Products for Veterinary Use

- 2.1 Legislation relevant to VPA holders and manufacturers of Veterinary Medicinal Products
- 2.2 Legislation specifically relevant to manufacturers of Veterinary Medicinal Products
- 2.3 Legislation relevant to distributors of veterinary medicinal products

1. Medicinal Products for Human Use

- 1.1 Legislation Relevant to Manufacturers of Medicinal Products for Human Use

European Legislation

- 1) Directive 2001/83/EC as amended by Directive 2004/27/EC

The requirement for the manufacture of medicinal products to be carried out in accordance with a Manufacturer's Authorisation (Licence) is set out in Article 40 of Directive 2001/83/EC as amended by Directive 2004/27/EC.

Additionally, Article 112 states that:

Member States shall take all appropriate measures to ensure that the holder of the marketing authorisation for a medicinal product and, where appropriate, the holder of the manufacturing authorisation, furnish proof of the controls carried out on the medicinal product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Article 8(3)(h).

Furthermore, Article 46 states that the holder of a manufacturing authorisation shall at least be obliged:

(f) to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.

This point may also be applicable to certain excipients, the list of which as well as the specific conditions of application shall be established by a Directive adopted by the commission in accordance with the procedure referred to in Article 121(2).

Article 47 states that:

The principles and guidelines of good manufacturing practices for medicinal products referred to in Article 46(f) shall be adopted in the form of a directive in accordance with the procedure referred to in Article 121(2).

Detailed guidelines in line with those principles will be published by the Commission and revised as necessary to take account of technical and scientific progress.

The principles of good manufacturing practice for active substances used as starting materials referred to in point (f) of Article 46 shall be adopted in the form of detailed guidelines.

The Commission shall also publish guidelines on the form and content of the authorisation referred to in Article 40(1), on the reports referred to in Article 111(3) and on the form and content of the certificate of good manufacturing practice referred to in Article 111(5).

The Directive referred to in Article 47 was published as Commission Directive 91/356/EC. Directive 91/356/EC was adopted for the purposes of introducing the concept of a pharmaceutical quality assurance system and is known as *The GMP Directive*. Directive 91/356/EC was replaced by Directive 2003/94/EC in May 2004, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

With reference to the recall of medicinal products, Article 13 of Directive 2003/94/EC states that:

The manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling promptly, and at any time, the medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated

by the manufacturer. The manufacturer shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination

The guidelines referred to in Directive 2003/94/EC, together with additional guidance notes, have been published as the European Community Guide to Good Manufacturing Practice (GMP) – Volume IV of the Rules Governing Medicinal Products.

Article 117 of Directive 2001/83/EC as amended by directive 2004/27/EC refers to the prohibition on the supply of a medicinal product and withdrawal of the medicinal product from the market if:

- (a) the medicinal product is harmful under normal conditions of use; or
- (b) it lacks therapeutic efficacy; or
- (c) the risk-benefit balance is not favourable under the authorised conditions of use; or
- (d) its qualitative and quantitative composition is not as declared; or
- (e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

Part (e) includes the failure to comply with the principles of Good Manufacturing Practice as published in the European Community Guide to Good Manufacturing Practice (GMP) – Volume IV of the Rules Governing Medicinal Products.

(2) European Community Guide to Good Manufacturing Practice (GMP) – Volume IV of the Rules Governing Medicinal Products

In Chapter 1, titled 'Quality Management', one of the basic requirements of GMP is that "a system is available to recall any batch of product from sale or supply".

Chapter 8 of the Guide contains text relevant to product recalls and is reproduced in Appendix III of this Guidance Note.

Chapter 8, titled 'Complaints and Product Recall' includes separate sections on complaints and on recalls. The section on complaints requires a manufacturer to inform the competent authority in relation to a quality defect which could lead to a recall or an abnormal restriction on supply of a medicinal product.

The section on recalls covers a number of aspects of this topic and stipulates the establishment of written procedures, the prompt initiation of recall activities, the informing of competent authorities in all appropriate countries, and the maintenance of good distribution records to ensure traceability of the product to be recalled.

Article 118 of Directive 2001/83/EC as amended states that:

1. The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.
2. In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.

Article 126 ensures that any request by a Competent Authority regarding market action is properly founded. It states that;

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.

National Legislation

(3) Medicinal Products (Control of Manufacture) Regulations 2007 (S.I. No. 539)

The relevant requirements of Directives 2003/94/EC and 2001/83/EC as amended by directive 2004/24/EC are transposed in the Medicinal Products (Control of Manufacture) Regulations 2007.

With regard to the recall of medicinal products, Schedule I paragraph 10, requires that the following particulars must accompany an application for a manufacturer's authorisation;

10 (d). A description of the arrangements for the withdrawal or recall from sale, supply or exportation of any medicinal product to which the authorisation relates, as may be required.

Further to that, Schedule 2– Authorisation holder manufacturing medicinal products, requires that;

13. The authorisation holder shall keep such documents as will facilitate the withdrawal or recall from sale, supply or exportation of any medicinal product to which the authorisation relates. Such documents shall be readily available for inspection by an authorised officer.

27. Where the authorisation holder has been informed by the Board that any part of a batch of a medicinal product to which his authorisation relates has been found not to conform as regards strength, quality or purity with the specifications of the relevant product he or she shall, if so directed by the Board, immediately withhold the remainder of that batch from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies already sold, supplied or exported from that batch.

28. Where the authorisation holder has been informed by the Board that a medicinal product to which his or her authorisation relates has been found to give rise to concerns in regard to its safety or efficacy, he or she shall, if so directed by the Board, immediately withhold that product from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such product already sold, supplied or exported.

29. Where the authorisation holder has been informed by the Board that any batch of a medicinal product, or part thereof, to which his authorisation relates, has not been manufactured in accordance with the principles and guidelines of good manufacturing practice set out in the GMP Directive, he or she shall, if so requested by the Board, immediately withhold that product from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such product already sold, supplied or exported.

30. Where the authorisation holder decides for whatever reason to recall a particular batch of a medicinal product manufactured by him or her, or part thereof, he or she shall forthwith inform the Board of the decision to recall and of the reason for such recall.

31. Where the authorisation holder considers that there may be grounds for the recall, or for the imposition of an abnormal restriction on the supply of a particular medicinal product manufactured by him or her, or of a batch or part of batch thereof, he or she shall consult with the Board in relation to the action which may be considered appropriate in the circumstances.

Legislation relevant to Manufacturers importing from a third country

National Legislation

Medical Products (Control of Wholesale Distribution) Regulations, 2007 (S.I No. 538 of 2007)

Schedule 3- Requirements to be met by an authorisation holder importing medicinal products from a third country

9. The authorisation holder shall keep such documents as will facilitate the withdrawal or recall from sale, supply or exportation of any medicinal product to which the authorisation relates. Such documents shall be readily available for inspection by an authorised officer.

18. Where the authorisation holder has been informed by the Board that any part of a batch of a medicinal product to which his or her authorisation relates has been found not to conform as regards strength, quality or purity with the specifications of the relevant product, he or she shall, if so directed by the Board, immediately withhold the remainder of that batch from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies already sold, supplied or exported from that batch.

19. Where the authorisation holder has been informed by the Board that a medicinal product to which his or her authorisation relates has been found to give rise to concerns in regard to its safety or efficacy, he or she shall, if so directed by the Board, immediately withhold that product from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such product already sold, supplied or exported.

20. Where the authorisation holder has been informed by the Board that any batch of a medicinal product, or part thereof, to which his or her authorisation relates, has not been manufactured in accordance with the principles and guidelines of good manufacturing practice set out in the GMP Directive, he or she shall, if so requested by the Board, immediately withhold that product from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such product already sold, supplied or exported.

21. Where the authorisation holder decides for whatever reason to recall a particular batch of a medicinal product imported by him or her, or part thereof, he or she shall forthwith inform the Board of the decision to recall and of the reason for such recall.

22. Where the authorisation holder considers that there may be grounds for the recall, or for the imposition of an abnormal restriction on the supply of a particular medicinal product imported by him or her, or of a batch or part of batch thereof, he or she shall consult with the Board in relation to the action which may be considered appropriate in the circumstances.

With regards to quality defects where the authorisation holder sells or supplies an exempt medicinal product, Schedule 3 paragraph 25 states that he or she shall maintain written records relating to –

25. 3(c) details of any quality defect relating to the product so sold or supplied of which he or she becomes aware.

Also subparagraphs 5 and 7 of paragraph 25 state that;

25. (5) The authorisation holder shall inform the Board forthwith of any matter, including suspected adverse reactions and quality defects, coming to his or her attention, in respect of an exempt medicinal product imported by him or her.

25. (7) The authorisation holder shall, on being informed by the Board, or by the manufacturer or person who supplied the medicinal product for importation, that the medicinal product

can not be regarded either as a product which can safely be administered to human beings or as a product which is of satisfactory quality or efficacy for such administration, immediately withdraw any supplies of that product held by him or her and immediately recall all supplies already sold or distributed.

1.2 Legislation Relevant to Marketing Authorisation Holders of Medicinal Products for Human Use

European Legislation

1) Directive 2001/83/EC as amended

"Directive 2001/83/EC as amended, on the Community code relating to medicinal products for human use" covers the marketing, manufacture and wholesaling of medicinal products for human use.

Article 116 of 2001/83/EC as amended by directive 2004/27/EC states that:

The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is harmful under normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under the normal conditions of use, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

An authorisation shall also be suspended, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10, 10a, 10b, 10c and 11 are incorrect or have not been amended in accordance with Article 23, or where the controls referred to in Article 112 have not been carried out.'

Furthermore Article 117 of 2001/83/EC as amended by directive 2004/27/EC states that:

1. Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

- (a) the medicinal product is harmful under normal conditions of use; or
- (b) it lacks therapeutic efficacy; or 30.4.2004 EN Official Journal of the European Union L 136/55
- (c) the risk-benefit balance is not favourable under the authorised conditions of use; or
- (d) its qualitative and quantitative composition is not as declared; or

(e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.

Article 118 of Directive 2001/83/EC as amended states that:

1. The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.

2. In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.

Article 123 of Directive 2001/83/EC as amended states that:

1. Each Member State shall take all the appropriate measures to ensure that decisions authorising marketing, refusing or revoking a marketing authorisation, cancelling a decision, refusing or revoking a marketing authorisation, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency (European Medicines Evaluation Agency) forthwith.

2. The marketing authorisation holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.

3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may effect the protection of public health in third countries is forthwith brought to the attention of the World Health Organisation, with a copy to the Agency.

4. The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.

Article 126 ensures that any request by a Competent Authority regarding market action is properly founded. It states that;

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.

National Legislation

2) Medicinal Products (Control of Placing on the Market) Regulations 2007 (SI No. 540 of 2007)

For PA holders, the above Directive requirements have been transposed into national law in these Regulations. These include the General Conditions applicable to Product Authorisations. A number of these Conditions set out requirements relating to compliance with the product authorisation, the provision to the Authority (HPRA) of any additional information which may alter the validity of data provided in support of the PA application and the collecting and reporting to the Authority of adverse reactions. Requirements relating to the withdrawal or recall of medicinal products are set out below;

Part 2 – Authorisation and Certification for Placing on the Market

Section 14- Revocation, suspension, or variation of an Authorisation or the suspension of the use or marketing of medicinal products

(5) Where, under the preceding provisions of this Regulation or the provisions of Regulation (EC) No 726/2004, the Board or the Commission revokes or suspends a marketing authorisation or Community marketing authorisation or the Board revokes or suspends a certificate of registration or certificate of traditional-use registration, or where the Board suspends the use, supply or placing on the market of a medicinal product, or where the relevant Community provisions so permit or require, the Board may and where appropriate, shall give written notice to the person who is or, immediately before its revocation or suspension, was the holder of the authorisation or certificate, requiring him or her to take all reasonable practicable steps to—

(a) inform wholesalers, pharmacies, retailers, practitioners, patients and others who may be in possession of the relevant products, of the revocation or suspension, the reasons for it, and the action, if any, to be taken to restrict or prevent further use, supply or marketing;

(b) withdraw from the market in the State and recover possession of such products within the time and for the period specified in the notice.

(6) The Board may require the holder of the marketing authorisation, certificate of registration or certificate of traditional-use registration, to withdraw from the market in the State specified batches only of a medicinal product to which a notice under paragraph (5) applies.

Part 3 – Obligations of Persons Placing Medicinal Products on the Market

Section 15 – General obligations

(2) Every holder of a marketing authorisation, certificate of registration or certificate of traditional-use registration, shall—

(c) keep such documents as will facilitate the withdrawal or recall from sale or supply of any medicinal product to which the authorisation or certificate relates.

(6) The holder of a marketing authorisation, certificate of registration or certificate of traditional-use registration shall promptly—

(j) inform the Board of any defect that could result in a recall or abnormal restriction on supply of the medicinal product concerned.

1.3 Legislation Relevant to Wholesalers of Medicinal Products for Human Use

European Legislation

(1) Directive 2001/83/EC

Directive 2001/83/EC as amended by Directive 2004/27/EC on the Community code relating to medicinal products for human use includes requirements for control over the entire chain of distribution of medicinal products within Member States and between Member States.

Article 80 (d), (e) and (f) of Directive 2001/83/EC states:

Holders of the distribution authorisation must fulfill the following minimum requirements:

(d) they must have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or holder of the marketing authorisation for the product concerned;

(e) they must keep records either in the form of purchase/sales invoices, or on computer, or in any other form giving for any transaction in medicinal products received or dispatched at least the following information:

- date,
- name of the medicinal product,
- quantity received or supplied,
- name and address of the supplier or consignee, as appropriate;

(f) they must keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years;

In addition, Article 82 states that:

For all supplies of medicinal products to a person authorised or entitled to supply medicinal products to the public in the Member State concerned, the authorised wholesaler must enclose a document that make it possible to ascertain:

- the date,
- the name and pharmaceutical form of the medicinal product,
- the quantity supplied,
- the name and address of the supplier and consignor.

Member States shall take all appropriate measures to ensure that persons authorised or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.

Article 80(g) of Directive 2001/83/EC sets out the requirement that wholesalers of medicinal products for human use must comply with the Guidelines on Good Distribution Practice of Medicinal Products for Human Use. These EU guidelines (hereafter referred to as the GDP guidelines) form the basis for Quality Systems for Wholesalers. Compliance with the GDP guidelines is the minimum requirement that a wholesaler must meet in order for a wholesaler's licence to be issued by HPRA and maintained.

(2) EU Guidelines on Good Distribution Practice (GDP) of Medicinal Products for Human Use (94/C 63/03)

Paragraphs 25-30 (inclusive) of these guidelines set out the obligations of the wholesaler in relation to "Emergency plan and recalls". These paragraphs of the Guidelines on Good Distribution Practice of Medicinal Products for Human Use are reproduced as Appendix IV.

In addition, paragraphs 7 and 8 of the GDP guidelines specify the types of records which should be kept and focus on the need for batch traceability in manufacturer to wholesaler, and wholesaler to wholesaler, transactions:

7. Records should be made at the time each operation is taken in such a way that all significant activities or events are traceable. Records should be clear and readily available. They should be retained for a period of five years at least.

8. Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the medicinal product and quantity received or supplied and name and address of the supplier or consignee. For transactions between manufacturers and wholesalers and between wholesalers (i.e. to the exclusion of deliveries to persons entitled to supply medicinal

products to the public), records should ensure the traceability of the origin and destination of products, for example by use of batch numbers, so that all the suppliers of, or those supplied with, a medicinal product can be identified.

Article 126 ensures that any request by a Competent Authority regarding market action is properly founded. It states that;

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.

National Legislation

(3) Medicinal Products (Control of Wholesale Distribution) Regulations, 2007 (S.I No. 538 of 2007)

For Irish wholesalers, the above Directive requirements have been transposed into national law in the Medical Products (Control of Wholesale Distribution) Regulations, 2007 (S.I No.538 of 2007) under Schedules 1 and 2.

Schedule 1 – Particulars That Must Accompany an Application for a Wholesaler's Authorisation

Paragraph 4, subparagraph (4) requires an applicant applying for a Wholesalers Authorisation to supply -

4. (4) A statement in the form of an emergency plan, setting out the procedures to be implemented in the event of both urgent and non-urgent recalls of medicinal products from the market.

Schedule 2 – Requirements to Be Met By the Authorisation Holder

Paragraphs 9, 13, 14, 15 and 17 of Schedule 2 outline the requirements relating to recalls and quality defects;

9. The authorisation holder shall have an emergency plan which will ensure the effective implementation of any recall from the market of any such product, or batch thereof, that may be ordered by the Board or carried out in cooperation with the manufacturer or holder of the marketing authorisation for the medicinal product concerned.

13. The authorisation holder shall comply with the principles and guidelines of good distribution practice for medicinal products⁸ published by the Commission under Article 84 of the 2001 Directive.

14. The authorisation holder shall, on being informed by the Board or by the holder of the marketing authorisation, that any batch of any medicinal product to which the wholesaler's authorisation relates, has been found not to conform as regards the provisions of the relevant marketing authorisation, or as regards the strength, quality or purity with the appropriate specification for that product, if so directed, immediately withhold such batch from sale or exportation, and if so directed by the Board, insofar as may be reasonably practicable, immediately withdraw from sale any supplies of that batch held by him or her and immediately recall all supplies already sold or distributed from that batch.

15. The authorisation holder shall, on being informed by the Board that a medicinal product to which the wholesaler's authorisation relates, has been found to give rise to concerns in regard to its safety or efficacy, if so directed by the Board, immediately withhold such product from sale, supply or exportation and insofar as may be reasonably practicable, immediately recall all supplies already sold or distributed by him or her.

17. (3) Where the authorisation holder sells or supplies an exempt sourced medicinal product, he or she shall, in addition to those records mentioned in paragraph 8(1) and subparagraph (2), make and maintain written records relating to—

(a) the batch number of the batch of the product from which each sale or supply was made;

(c) details of any quality defect relating to the product so sold or supplied of which he or she becomes aware.

17. (5) The authorisation holder shall inform the Board forthwith of any matter, including suspected adverse reactions and quality defects, coming to his or her attention, in respect of an exempt sourced medicinal product that has been sourced by him or her.

17. (6) The authorisation holder shall cease supplying an exempt sourced medicinal product if he or she has received a notice in writing from the Board directing that, as from a date specified in that notice, a particular product or class of products shall no longer be sourced or supplied.

17. (7) The authorisation holder shall, on being informed by the Board, or by the manufacturer or person who supplied the medicinal product to the holder of the authorisation, that the medicinal product can not be regarded either as a product which can safely be administered to human beings or as a product which is of satisfactory quality or efficacy for such administration, immediately withdraw any supplies of that product held by him or her and immediately recall all supplies already sold or distributed.

2. Veterinary Medicinal Products

The following articles are relevant to the recall of veterinary medicinal products.

2.1 Legislation Relevant to Veterinary Product Authorisation Holders

European Legislation

(1) Directive 2001/82/EC

“Directive 2001/82/EC on the Community code relating to veterinary medicinal products” covers control over the marketing, manufacture and wholesaling of medicinal products for veterinary use within Member States.

Article 83 of Directive 2001/82/EC states:

1 ‘Member States’ competent authorities shall suspend, revoke, withdraw or vary marketing authorisations when it is clear that:’;

(a) the risk-benefit assessment of the veterinary medicinal product is, under the authorized conditions of use, unfavourable, particular regard being had to the benefits for animal health and welfare and to consumer safety, when the authorisation concerns a veterinary medicinal product for zootechnical use;

(b) the veterinary medicinal product does not have any therapeutic effect on the species of animal for which the treatment is intended;

(c) its qualitative and quantitative composition is not as stated;

(d) the recommended withdrawal period is inadequate to ensure that foodstuffs obtained from the treated animal do not contain residues which might constitute a health hazard to the consumer;

(e) the veterinary medicinal product is offered for sale for a use which is prohibited by other community provisions.

Article 84 of Directive 2001/82/EEC states that:

1. Without prejudice to Article 83, Member States shall take all necessary measures to ensure that supply of a veterinary medicinal product is prohibited and that the medicinal product concerned is withdrawn from the market where:

(a) it is clear that the risk-benefit assessment of the veterinary medicinal product is, under the authorized conditions of use, unfavourable, particular regard being had to the benefits for animal health and welfare and to the safety and health benefits for the consumer, when the authorisation concerns a veterinary medicinal product for zootechnical use;

(b) the veterinary medicinal product has no therapeutic effect on the species of animal for which the treatment was intended;

(c) the qualitative and quantitative composition of the veterinary medicinal product is not as stated;

(d) the recommended withdrawal period is inadequate to ensure that foodstuffs obtained from the treated animal do not contain residues which might constitute a health hazard to the consumer;

(e) the control tests referred to in Article 81(1) have not been carried out, or any other requirement or obligation relating to the grant of the manufacturing authorization referred to in Article 44 (1) has not been complied with.

2. The competent authority may confine the prohibition on supply and withdrawal from the market solely to the contested production batches.

Article 91 of Directive 2001/82/EEC states that:

1. Each Member State shall take all appropriate measures to ensure that the Agency is informed immediately of decisions granting marketing authorisation and of all decisions refusing or withdrawing marketing authorisation, cancelling a decision, refusing or withdrawing marketing authorisation, prohibiting supply or withdrawing a product from the market, together with the reasons on which such decisions are based.

2. The marketing authorisation holder shall be obliged to notify the Member States forthwith of any action taken by him to suspend the marketing of a veterinary medicinal product or to withdraw a product from the market, together with the reasons for such action if it concerns the effectiveness of the veterinary medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.

3. Member States shall ensure that appropriate information about actions taken pursuant to paragraphs 1 and 2 which may affect the protection of health in third countries is forthwith brought to the attention of the relevant international organisations, with a copy to the Agency.

National Legislation

(2) Animal Remedies (No. 2) Regulations, 2007 (SI No. 786 of 2007).

For Veterinary Product Authorisation Holders, the above Directive requirements have been transposed into national law in the Animal Remedies Regulations, 2007 (SI No. 786 of 2007) regulations 12 and 14 which state, inter alia:

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(2) (b) An animal remedies authorisation shall not be revoked, varied or suspended until the representations, if any, of the holder of the animal remedies authorisation have been considered.

(c) Notwithstanding sub-paragraph (b), in case of urgency if public or animal health is threatened, the Board may suspend the distribution, sale and supply of an animal remedy.

(8) A person who sells or supplies an animal remedy shall notify the Board of any action taken by him or her to—

(a) suspend the sale or supply, or

(b) recall,

an animal remedy together with the reasons for the action if it concerns the efficacy or safety (including the protection of public health) of the animal remedy.

14 Recall of an animal remedy

(1) The Board may, by notice ("recall notice"), order the recall of any animal remedy or a batch of an animal remedy if it is of the opinion that –

(a) a circumstance referred to in Article 84(1) of the Directive applies

(b) an animal remedy consists of or contains a substance the administration of which, to a class of animal for which the animal remedy is intended, is unlawful

(c) the animal remedy is not manufactured in accordance with the animal remedies authorisation or in accordance with the principles and guidelines referred to in Article 50(f) of the Directive, or

(d) the animal remedy is not labelled in accordance with the animal remedies authorisation.

(2) The Board may modify or annul a recall notice.

(3) The Board may confine a recall notice to wholesaler or retailer level if it considers such action appropriate for the protection of animal or public health or environmental safety.

(4) A person shall comply with a recall notice (including a notice subject to representation under paragraph (8)).

- (5) If a recall notice is issued by the Board, the marketing authorisation holder shall consult with and agree to a requirement or amendment notified by the Board regarding the text of a recall notice or to the publication of the notice.
- (6) Records of the recall of an animal remedy shall be available for inspection by an authorised officer of the Board.
- (7) Without prejudice to paragraph (8), if the Board proposes to issue a recall notice, it shall –
- (a) notify the holder in writing of the proposal and of the reasons therefore, and that he or she may make representation to the Board in relation to the proposal within 7 days of the notification,
 - (b) consider a representation duly made before deciding whether to proceed with, modify or annul the proposal, and
 - (c) notify the holder of the decision and the reasons therefore, and the notice shall not have effect until the Board issues a notification of its decision in accordance with subparagraph (c).
- (8) If the Board, for urgent public or animal health reasons, issues a recall notice, it shall
- (a) notify the holder in writing of the decision and the reasons therefore, and that he or she may (without prejudice to paragraph (4)) make representations to the Board in relation to the decision within 14 days of the date of the notification,
 - (b) consider a representation duly made, and
 - (c) confirm, modify or annul the decision and notify the holder of the decision and the reasons therefore.

2.2 Legislation Specifically Relevant to Manufacturers of Veterinary Medicinal Products

European Legislation

- (1) Directive 2001/82/EC

The requirement for the manufacture of veterinary medicinal products to be carried out in accordance with a Manufacturer's Authorisation is set out in Article 44 of Directive 2001/82/EC.

Article 84 of Directive 2001/82/EC refers to the prohibition on the supply of a veterinary medicinal product and withdrawal of the veterinary medicinal product from the market if:

- (e) the control tests referred to in Article 81(1) have not been carried out, or any other requirement or obligation referred to in Article 44(1) has not been complied with

Article 50 states that the holder of a manufacturing authorisation shall at least be obliged to:

- (f) comply with the principles and guidelines on good manufacturing practice for medicinal products and use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing for starting materials.

Article 51 states that:

The principles and guidelines of good manufacturing practice for veterinary medicinal products referred to in Article 50 (f) shall be adopted in the form of a Directive addressed to the Member States in accordance with the procedure referred to in Article 89 (2).

Detailed guidelines shall be published by the Commission and revised as appropriate to take account of scientific and technical progress.

The Directive referred to in Article 51 was published as Commission Directive 91/412/EC. Directive 91/412/EC was adopted for the purposes of introducing the concept of a pharmaceutical quality assurance system to the manufacture of veterinary medicinal products.

(2) European Community Guide to Good Manufacturing Practice (GMP) – Volume IV of the Rules Governing Medicinal Products

With reference to the recall of medicinal products, Article 13 of Directive 91/412/EC states that:

The manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time the veterinary medicinal products in the distribution network. Any complaint concerning a quality defect shall be recorded and investigated by the manufacturer. The competent authority shall be informed by the manufacturer of any quality defect that could result in a recall or abnormal restriction on the supply. In so far as possible, the countries of destination shall also be indicated. Any recall shall be made in accordance with the requirements referred to in Article 91 of Directive 2001/82/EC (Pharmacovigilance).

The contents of Directive 91/412/EC have been published as the European Community Guide to Good Manufacturing Practice (GMP) – Volume IV of the Rules Governing Medicinal Products already referred to in this Guidance Note in section 1.1.2 above. This Guide is applicable to the manufacture of medicinal products for both human and veterinary use. Chapter 8 of the Guide, relevant to product recalls, is reproduced in Appendix III.

In Chapter 1, titled 'Quality Management', one of the basic requirements of GMP is that "*a system is available to recall any batch of product from sale or supply*".

Chapter 8, titled "Complaints and Product Recall" includes separate sections on Complaints and on Recall. The section on Complaints requires a manufacturer to inform the competent authority in relation to a quality defect which could lead to a recall or an abnormal restriction on supply of a medicinal product. The section on Recall covers a number of aspects of this topic, and stipulates the establishment of written procedures, the prompt initiation of recall activities, the informing of competent authorities in all appropriate countries, and the

maintenance of good distribution records to ensure traceability of the product to be recalled. Sections relevant to 'Complaints and Product Recall' are discussed previously in section 1.1.2.

National Legislation

Animal Remedies (No. 2) Regulations, 2007 (SI No. 786 of 2007).

Schedule 5 Requirements to be met by a holder of a manufacturer's licence

12. The license holder shall keep such documents as will facilitate the withdrawal or recall from sale, supply or exportation of an animal remedy to which the license relates. The documents shall be readily available for inspection by an authorised officer.

19. If the license holder has been informed by the Board that any part of a batch of an animal remedy to which his or her license relates has been found not to conform as regards strength, quality or purity with the specifications of the relevant product, he or she shall, if so directed by the Board, immediately withhold the remainder of that batch from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies already sold, supplied or exported from that batch.

20. If the license holder has been informed by the Board that any part of a batch of an animal remedy to which his or her license relates has been found to give rise to unacceptable adverse reactions, he or she shall, if so directed by the Board, immediately withhold the remainder of that batch from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies already sold, supplied or exported

21. If the licence holder has been informed by the Board that any batch of an animal remedy, or part thereof, to which his or her license relates, has not been manufactured in accordance with the principles and guidelines of good manufacturing practice, he or she shall, if so requested by the Board, immediately withhold that product from sale, supply or exportation, insofar as may be practicable, immediately recall all supplies of the product already sold, supplied or exported.

22. If the licence holder recalls a particular batch of an animal remedy manufactured by him or her, or part thereof, he shall forthwith inform the Board of the decision to recall and of the reason for such recall.

23. If the license holder considers that there may be grounds for the recall, or for the imposition of an abnormal restriction on the supply of an animal remedy manufactured by him or her, or of a batch or part of a batch thereof, he or she shall consult with the Board in relation to the action which may be considered appropriate in the circumstances.

2.3 Legislation Relevant to Wholesalers of Veterinary Medicines

European Legislation

(1) Directive 2001/82/EC

"Directive 2001/82/EC on the Community code for veterinary medicinal products" includes requirements for control over the entire chain of distribution of medicinal products within Member States and between Member States.

Article 65.3 of Directive 2001/82/EC states:

3. The holder of the authorisation for distribution shall be required to keep detailed records. The following minimum information shall be recorded in respect of each incoming or outgoing transaction:

- (a) date;
- (b) precise identity of the veterinary medicinal product;
- (c) manufacturer's batch number, expiry date;
- (d) quantity received or supplied;
- (e) name and address of the supplier or recipient.

At least once a year a detailed audit shall be carried out to compare incoming and outgoing medicinal supplies with supplies currently held in stock, any discrepancies being recorded.

These records shall be available for inspection by the competent authorities for a period of at least three years.

National Legislation

Animal Remedies Regulations, 2007 (SI No. 786 of 2007)

For Irish wholesalers of veterinary medicinal products, the above Directive requirements have been transposed into national law in the Animal Remedies Regulations, 2007 (SI No. 786 of 2007) regulation 30, Wholesale of Animal Remedies, section (5) which states, inter alia:

- (5) Without prejudice to Regulation 49, the holder of an animal remedies wholesalers license, shall –
 - (d) immediately withdraw, if directed by the Minister, the Agency, the Board or the marketing authorisation holder, from sale or supply any quantity and, in so far as is practicable, immediately recall any quantity sold or supplied of –
 - (i) a batch or part of a batch of an animal remedy that does not conform with an animal remedies authorisation, or the strength, quality or purity, does not conform with the specification of that animal remedy, or

- (ii) an animal remedy that has given rise to unacceptable adverse reactions,
- (e) keep, at the premises to which the license refers, records of purchase and sale invoices in respect of each incoming and outgoing transaction detailing at least the following information –
 - (i) the date of transaction;
 - (ii) the precise identity of the animal remedy including name and pharmaceutical form and pack sizes;
 - (iii) the manufacturer's batch number and expiry date;
 - (iv) the quantity received or supplied;
 - (v) the name and address of the supplier or consignee;
 - (vi) quantities received and returned in accordance with subparagraph (k)
- (f) keep at his or her premises the records referred to in subparagraph (e) for a period of five years from the date of receipt, sale or supply of the animal remedy and these records shall be made available to an authorized officer on request

The Animal Remedies Regulations, 2007 (SI No. 786 of 2007), regulation 31, states the requirements for holders of animal remedies merchants licenses relating to recalls:

31 Retail sale of an animal remedy

(5) Without prejudice to Regulation 49, the holder of an animal remedies merchant's licence, shall –

(f) immediately withdraw, if directed by the Minister, the Agency, the Board, the marketing authorisation holder or the holder of an animal remedies wholesale license, from sale or supply any quantity, and, in so far as is practicable, immediately recall any quantity sold or supplied of –

(i) a batch or part of a batch of an animal remedy found not to conform with an animal remedies authorisation or as regards strength, quality or purity, with the specification of that animal remedy, or

(ii) an animal remedy found to give rise to unacceptable adverse reactions

(10) This Regulation does not apply to –

(a) a pharmacy, or

(b) a part of a premises, which is not a retail outlet to which this Regulation applies, used by a registered veterinary practitioner, in respect of which a certificate of suitability has been granted or deemed to have been granted under Part 9 of the Veterinary Practice Act 2005 (No. 22 of 2005).

2.4 Miscellaneous

National Legislation

Animal Remedies Regulations, 2007 (SI No. 786 of 2007)

47 Information to the Agency.

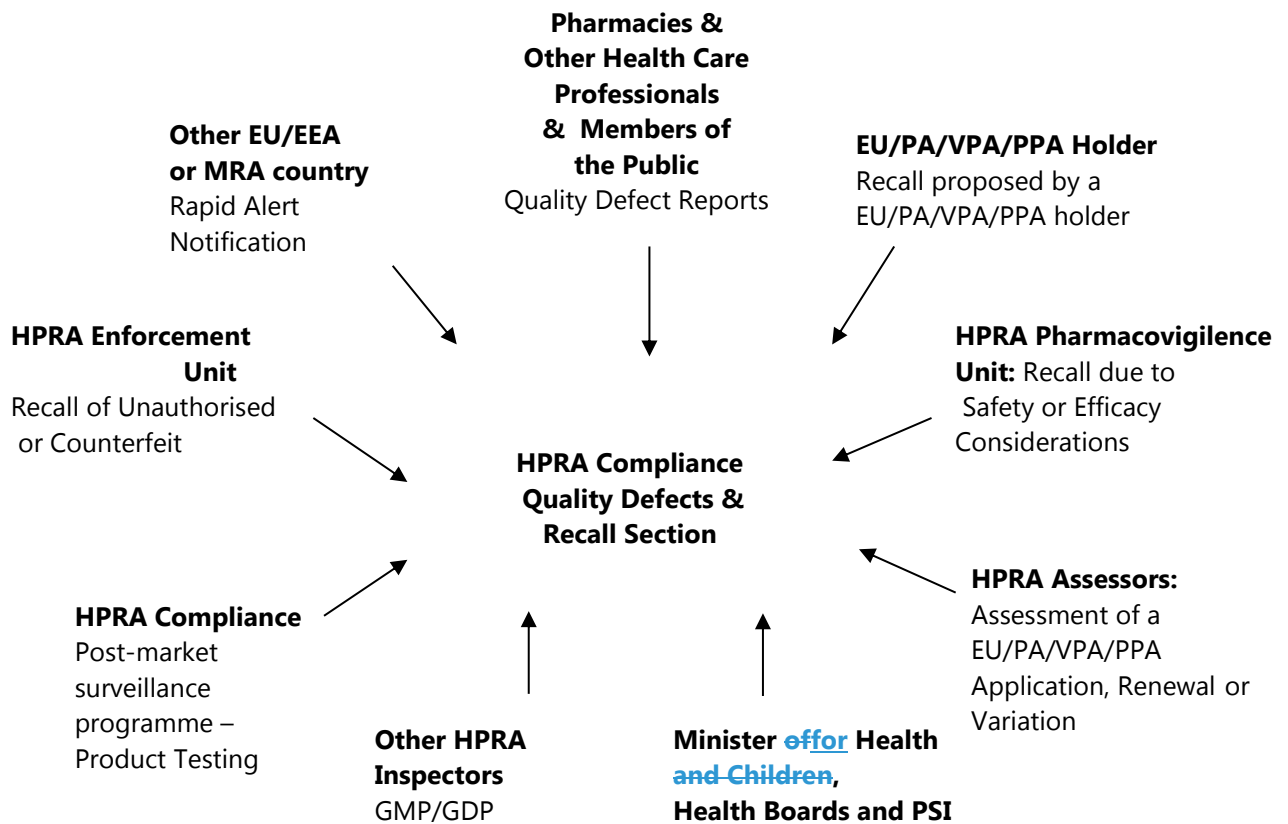
(1) The Board shall inform the Agency of a decision to grant, refuse, suspend or revoke a veterinary product authorisation or a manufacturer's license, or to prohibit the sale or supply, or to recall an animal remedy and the reasons for the decision.

(3) The Board shall ensure that appropriate information about actions taken pursuant to paragraph (1) or Regulation 12, which may affect the protection of health in a third country, is brought to the attention of the relevant international organisations and the Agency.

APPENDIX II POSSIBLE SOURCES OF PRODUCT RECALL NOTIFICATIONS

A potential recall issue can be brought to the attention of a EU/PA/VPA/PPA holder, manufacturer, wholesaler, or directly to the Compliance department of the HPRA, from a variety of sources as detailed in Figure 2.0 below. Explanatory information relating to each of these sources of product recall notifications is given on the next two pages.

Figure 2.0 Possible Sources of Product Recall (and Potential Recall) Notifications Received by HPRA



Appendix II Cont'd

1) Rapid Alert Communications from another Competent Authority

The Rapid Alert is a fax or electronic message sent by an EU/European Economic Area (EEA) and/or Pharmaceutical Inspection Co-operation Scheme (PIC/S) Member State, or a Mutual Recognition Agreement (MRA) partner, to other Member States, or MRA partners, in the event of a recall in the first Member State which may have implications in other Member States.

2) Quality Defect Reports

These may be received by the HPRA Compliance from EU/PA/VPA/PPA holders, manufacturers, wholesalers, pharmacists and patients / users. Postage paid Quality Defect Report (QDR) Cards, currently referred to as 'Green' cards, are provided free to pharmacists by HPRA to facilitate the reporting of quality defects. A defect report may lead to a recall which is then overseen by the Compliance Department of the HPRA.

3) Reports of Product Recalls Initiated by the EU/PA/VPA/PPA Holder

A EU/PA/VPA/PPA holder may contact the HPRA stating that a decision has been taken to recall a batch or batches of a product.

4) Product withdrawal notifications due to safety or efficacy concerns

These will have been considered initially by the clinical assessors / pharmacovigilance section of the relevant Competent Authority, frequently in consultation with the EU Committee for Medicinal Products for Human Use (CHMP) or the EU Committee for Medicinal Products for Veterinary Use (CVMP), as appropriate. These committees are expert committees which operate at the European Medicines Agency (EMA).

5) Recommendations arising out of Good Manufacturing Practice (GMP) or Wholesale Good Distribution Practice (GDP) Inspections

A recall situation may arise where a GMP or wholesale GDP inspection reveals evidence that a product was not manufactured in accordance with acceptable standards of Good Manufacturing Practice or in accordance with its EU/PA/VPA/PPA, or was not stored or distributed in accordance with the labelled storage conditions for the product and / or in accordance with GDP.

6) Reports Arising out of the HPRA Assessment of Applications for Renewal or Variation of Product Authorisations

For example, updated stability information may show that a product is not of an acceptable stability to support its shelf life and a recall of batches on the market may be necessary.

7) Reports Arising from HPRA's Market Surveillance programme

Laboratory testing of product samples taken in the course of inspections or as part of the HPRA's market surveillance programme may show a batch to be of unacceptable quality.

8) Reports of Unauthorised or Counterfeit Medicinal Products

These notifications may be received from the Enforcement Unit of the HPRA (or other department within the HPRA).

9) Notifications Concerning Recalls Relating to Medicinal Products Exempt from Authorisation

These notifications concern medicinal products that are exempt from product authorisation requirements (i.e. products which are being supplied on foot of a prescription or order from a registered medical practitioner, veterinarian or dentist, or in accordance with the cascade system set out in Directive 2001/82/EC.)

APPENDIX III EUDRALEX – THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION, VOLUME 4, EU GUIDELINES TO GOOD MANUFACTURING PRACTICE – MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE.

Part I, Chapter 8 – “Complaints and Product Recall”

Principle

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. In order to provide for all contingencies, and in accordance with Article 117 of Directive 2001/83/EC and Article 84 of Directive 2001/82/EC, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

Complaints

- 8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the Qualified Person, the latter should be made aware of any complaint, investigation or recall.
- 8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- 8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control (QC) should normally be involved in the study of such problems.
- 8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.
- 8.5 All the decisions and measures taken as a result of a complaint should be recorded and references to the corresponding batch records.
- 8.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 8.7 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

- 8.8 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.

Recalls

- 8.9 A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation. If this person is not the Qualified Person, the latter should be made aware of any recall operation.
- 8.10 There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.
- 8.11 Recall operations should be capable of being initiated promptly and at any time.
- 8.12 All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.
- 8.13 The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, telephone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.
- 8.14 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 8.15 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.
- 8.16 The effectiveness of the arrangements for recalls should be evaluated regularly.

APPENDIX IV EMERGENCY PLANS AND RECALLS (SECTIONS 25 TO 30) OF THE EU GUIDELINES ON GOOD DISTRIBUTION PRACTICE OF MEDICINAL PRODUCTS FOR HUMAN USE (94/C 63/03)

Emergency Plan and Recalls

25. An emergency plan for urgent recalls and a non-urgent recall procedure should be described in writing. A person should be designated as responsible for execution and co-ordination of recalls.
26. Any recall operation should be recorded at the time it is carried out and records should be made available to the competent authorities of the Member States on whose territory the products were distributed.
27. In order to ensure the efficacy of the emergency plan, the system of recording of deliveries should enable all destinations of a medicinal product to be immediately identified and contacted. In case of recall, wholesalers may decide to inform all their customers of the recall or only those having received the batch to be recalled.
28. The same system should apply without any difference to deliveries in the Member States having granted the authorisation for wholesaling and in other Member States.
29. In case of batch recall, all customers (other wholesalers, retail or hospital pharmacists and persons entitled to sell medicinal products to the public) to whom the batch was distributed should be informed with the appropriate degree of urgency. This includes customers in Member States other than the Member State having granted the wholesaling authorisation.
30. The recall message approved by the holder of the marketing authorisation, and, when appropriate, by the competent authorities, should indicate whether the recall should be carried out also at retail level. The message should request that the recalled products be removed immediately from the saleable stock and stored separately in a secure area until they are sent back according to the instructions of the holder of the marketing authorisation.

APPENDIX V SAMPLE BATCH RECALL LETTER

[Company Headed Paper]

Batch Recall
Product Name, Pharmaceutical Form & EU/PA/VPA/PPA Number
Batch Number(s) and Expiry Date(s)

Date of Mailing

Dear Pharmacist/Doctor/Wholesaler (use as appropriate)

We wish to advise you that batch no. _____ of _____, EU/PA/VPA/PPA No. _____ is being recalled with immediate effect. *[If more than one batch is being recalled, a table showing the batch numbers may be appropriate here.]*

This recall is going to wholesale / pharmacy / retail / patient / user level. *[Delete as appropriate]*

This action has been agreed with the Health Products Regulatory Authority.

The reason for the recall is that _____

Please immediately quarantine any units of this batch which you have in your possession. [Instruction is now provided to the reader on the return or on the direct uplift of quarantined stock* It is appropriate to state here the last date by which recalled stock will be received back for credit. For retailers, this date could be two weeks from the date of receipt of the recall letter. For wholesalers, this could be four weeks. The purpose of having these dates specified is to help ensure the recall is completed expeditiously.]

If you have supplied this batch (these batches) to any other wholesaler, please fax those wholesalers a copy of this recall letter, requesting that they quarantine and return any unsold quantities of this batch (these batches) to you. *[Amend this section as appropriate – this paragraph only applies to wholesalers.]*

We apologise for any inconvenience this action may cause. Should you have any queries, please contact _____ at telephone number _____

Yours sincerely,

Name and Position, Tel. Number

* Notes:

Wholesalers are usually requested to return their quarantined units to their primary wholesaler. A Fax-Back form may be attached with the recall letter, so that wholesalers may notify their primary wholesaler by Fax of the number of units which are held in quarantine. Pharmacists are usually requested to return their quarantined units to their wholesaler. However, there are cases where quarantined items must be uplifted directly by a wholesaler or primary wholesaler – this is generally where the batch defect is of a serious nature. The Compliance Department will provide guidance in this regard.

If the recall will result in an out of stock situation arising in the marketplace, this should be stated in the letter. The Compliance Department will provide guidance on details which may need to be provided in this regard.

It is appropriate for the company to include a statement concerning the return of credit in the letter, if it wishes to do so.

* The author of the recall letter is requested to have an independent person check the draft letter for errors before it is sent to HPRA for final review. This independent person should be an employee of the company, but should ideally not have been involved in any part of the drafting of the letter. When submitting the letter to HPRA, the author should state in writing that the final draft version of the letter has been independently checked.

APPENDIX VI SAMPLE PRODUCT RECALL LETTER

[Company Headed Paper]

Product Recall

Product Name, Pharmaceutical Form & EU/PA/VPA/PPA Number

**All Batches distributed before _____
or Batches with an expiry date of _____ or earlier**

Date of Mailing

Dear Pharmacist/Doctor/Wholesaler (use as appropriate)

We wish to advise you that all in-date batches of _____, EU/PA/VPA/PPA No. _____ are being recalled with immediate effect.

This recall is going to wholesale / pharmacy / retail / patient level. *[Delete as appropriate]*

This action has been agreed with the Health Products Regulatory Authority.

The reason for the recall is that _____

Please immediately quarantine any units of this product which you have in your possession. [Instruction is now provided to the reader on the return or on the direct uplift of quarantined stock* It is appropriate to state here the last date by which recalled stock will be received back for credit. For retailers, this date could be two weeks from the date of receipt of the recall letter. For wholesalers, this could be four weeks. The purpose of having these dates specified is to help ensure the recall is completed expeditiously.]

If you have supplied this batch (these batches) to any other wholesaler, please fax those wholesalers a copy of this recall letter, requesting that they quarantine and return any unsold quantities of this batch (these batches) to you. *[Amend this section as appropriate – this paragraph only applies to wholesalers.]*

We are endeavouring to make replacement stock of this product available as soon as possible. It is expected that replacement stock will be available again in ___ weeks (or months). Until then, this product will be unavailable. *[See notes below]*

We apologise for any inconvenience this action may cause. Should you have any queries, please contact _____ at telephone number _____.

Yours sincerely,

Name and Position

Tel. Number

Notes: * Wholesalers are usually requested to return their quarantined units to their primary wholesaler. A Fax-Back form may be attached with the letter, so that wholesalers may notify their primary wholesaler by Fax of the number of units which are held in quarantine.

* Pharmacists are usually requested to return their quarantined units to their wholesaler.

However, there are cases where quarantined items must be uplifted directly by a wholesaler or primary wholesaler – this is generally where the batch defect is of a serious nature. The Compliance Department will provide guidance in this regard.

* It is appropriate for the company to include a statement concerning the return of credit in the letter, if it wishes to do so.

* The author of the recall letter is requested to have an independent person check the draft letter for errors before it is sent to HPRA for final review. This independent person should be an employee of the company, but should ideally not have been involved in any part of the drafting of the letter. When submitting the letter to HPRA, the author should state in writing that the final draft version of the letter has been independently checked.

APPENDIX VII SAMPLE CAUTION-IN-USE LETTER

[Company Headed Paper]

Caution-In-Use Notification

Product Name, Pharmaceutical Form & EU/PA/VPA/PPA Number

Batch Number (if appropriate)

Date of Mailing

Dear Pharmacist/Doctor/Health Care Professional *[use as appropriate]*

Following discussions with the Health Products Regulatory Authority, we wish to alert you of the following:

[The cautionary message is provided here.]

If the issue relates to a quality defect, it would be appropriate here to describe the defect, to state what batches are affected, and to provide the cautionary advice or instructions as agreed with the Compliance Department of the HPRA.

If the issue relates to something other than a quality defect, the Compliance Department will provide guidance on how best to address the issue.]

We are endeavouring to address this matter in the following way:

[Information would now be given in this regard. It may be appropriate to also provide information on replacement stock here.]

We apologise for any inconvenience this issue may cause. Should you have any queries, please contact _____ at telephone number _____.

Yours sincerely,

Name and Position
Tel. Number

Note:

Caution-In-Use letters are very much written and agreed on a case-by-case basis with HPRA. They are usually required in order to communicate the presence of a quality defect on a batch or product, when a batch or product recall is either not warranted or not possible. They may

also be used to communicate other issues to health care professionals, such as labelling similarity issues between medicinal products, before the labelling can be changed. The Compliance Department will provide detailed guidance on the information which may need to be provided in all Caution-In-Use communications.

The author of the CIUN is requested to have an independent person check the draft letter for errors before it is sent to HPRA for final review. This independent person should be an employee of the company, but should ideally not have been involved in any part of the drafting of the letter. When submitting the CIUN to HPRA, the author should state in writing that the final draft version of the CIUN has been independently checked.