HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Good Distribution Practice of Medicinal Products for Human Use

IA-G0046-~~6~~7
~~9 MARCH 2021~~
19 DECEMBER 2023

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

CONTENTS

1 SCOPE

The purpose of this document is to provide additional clarification to wholesalers and brokers located in Ireland regarding the Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 68/01). These guidelines, published by the European Commission, became effective on 8 September 2013. Due to some typographical errors in the guidelines, an updated version was published, Guidelines of 5 November 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01), available on the European Commission website, (hereafter referred to as 'the guidelines').

Good distribution practice (GDP) requirements clearly outlined in the guidelines are not repeated within this guidance document as the requirements are deemed to be self-explanatory and do not need additional clarification within this document. Wholesalers should ensure that they comply in full with all requirements of both the guidelines and this HPRA guidance document. Wholesalers should ensure that documentation is made available to the HPRA to verify compliance with GDP requirements, when requested.

The licensing authority for the wholesaling of medicinal products for veterinary use is the Department of Agriculture, Food and the Marine; this guide does not relate to the wholesale of veterinary medicinal products.

For companies wishing to apply for a wholesale distribution authorisation (WDA) or to register as a broker, please refer to 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland' available in the 'Publications and Forms' section at www.hpra.ie.

2 INTRODUCTION

'Sale by wholesale' means sale or supply for the purposes of sale, in the course of a business or for administration to patients in the course of a professional practice. Wholesale distribution includes all activities consisting of procuring, holding, supplying or exporting medicinal products, other than activities involving the sale or supply of such products to the public (Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended and Directive 2001/83/EC).

Persons who, in the course of a business, whether acting as sole traders, in partnerships, or in limited liability companies, are engaged in wholesale distribution of medicinal products for human use, require a wholesale distribution authorisation (WDA), unless exempt under the Regulations, and must comply with the relevant Regulations, Directives and guidelines. The HPRA has published guidance on the activities and operations that require a WDA in Ireland, in the 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland'. The HPRA can only grant a WDA to companies that conduct wholesaling activities in Ireland.

'Brokering of medicinal products' means all activities in relation to the sale or purchase of medicinal products, except for wholesale distribution and sale by wholesale, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person. Brokers of medicinal products located in Ireland must be registered as a broker with the HPRA and must comply with the relevant Regulations, Directives and guidelines. The HPRA has published guidance on the activities and operations that constitute brokering of medicinal products in the 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland'.

3 ABBREVIATIONS

DPR	Dual pack import registration
EEA	European Economic Area
EMA	European Medicines Agency
EMP	Exempt medicinal product
EU	European Union
GDP	Good distribution practice
GMP	Good manufacturing practice
ICH	International Conference on Harmonisation
INCB	International Narcotics Control Board
HPRA	Health Products Regulatory Authority
MA	Marketing authorisation
MAH	Marketing authorisation holder
OCABR	Official Control Authority Batch Release
PA	Product authorisation
PPA	Parallel product authorisation
QP	Qualified Person
SOP	Standard operating procedure
RP	Responsible person
RPB	Retail Pharmacy Business
WDA	Wholesale distribution authorisation

4 LEGISLATIVE BASIS

At European level the legislative basis for wholesaling and brokering of medicinal products is detailed in Title VII of Directive 2001/83/EC of the Community code relating to medicinal products for human use.

The Medicinal Products (Control of Wholesale Distribution) Regulations 2013 transposed the requirements of Title VII of Directive 2001/83/EC into national legislation. In addition, these

Regulations consolidated and updated the requirements of previous legislation governing this area.

The requirement for brokers and wholesalers in Ireland to comply with the guidelines of GDP is laid down in Articles 80(g) and 85(b) of Directive 2001/83/EC and Schedule 2, Paragraph 13 of the Medicinal Products (Control of Wholesale Distribution) Regulations 2013.

Copies of the Irish Acts and Regulations referred to throughout this document are available to order from ~~publications@opw.ie~~publications@opw.ie or may be viewed and downloaded from the Attorney General's website.

5 EUROPEAN UNION GUIDELINES ON GOOD DISTRIBUTION PRACTICE OF PRODUCTS FOR HUMAN USE

The full text of the 'Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use' is available on the European Commission website.
The guidelines are structured into a number of chapters, which cover the necessary components for wholesalers and brokers to comply with GDP and include the following:

INTRODUCTION

CHAPTER 1 QUALITY MANAGEMENT
- Principle
- Quality system
- Management of outsourced activities
- Management review and monitoring
- Quality risk management

CHAPTER 2 PERSONNEL
- Principle
- Responsible person
- Other personnel
- Training
- Hygiene

CHAPTER 3 PREMISES AND EQUIPMENT
- Principle
- Premises
- Equipment

CHAPTER 4 DOCUMENTATION
- Principle
- General

The following guidance is an elaboration of some of the content of the GDP guidelines and should be read in conjunction with the guidelines.

CHAPTER 1 QUALITY MANAGEMENT

Quality management

If a wholesaler is acting as a primary distributor, technical agreements should be in place with the marketing authorisation holder (MAH). These technical agreements should at least describe the GDP roles and responsibilities of both parties including details on transportation arrangements, receipt of goods, batch release arrangements, verification of safety features, customer approval, documentation, recalls, returns, customer complaints, suspected falsified medicinal products, and management of deviations and changes. The technical agreement serves as a basis for defining the division of GDP activities and responsibilities between the parties. However, it is important to highlight that the wholesaler retains ultimate responsibility for ensuring that the operations conducted are compliant with GDP and legal requirements. Technical agreements and procedures covering delegated activities may be reviewed during the course of a HPRA inspection.

Any wholesaler operating to other accredited quality standards should ensure that its operation also complies with the legislative and GDP guidelines governing the wholesale distribution of medicinal products. In such cases, the wholesaler should perform a gap analysis of the specific requirements relating to the distribution of medicinal products against its current operational standard. Differences in approach or gaps identified should be addressed through the introduction of additional procedures within the quality system as required.

Chapter 1 introduces a number of new concepts, which were not included within the previous EU GDP guidelines, including quality risk management, validation, change control, deviation and corrective and preventive action (CAPA) management. These requirements of GDP are further discussed later in this document.

Change control

The purpose of a change control system is to enable wholesalers to identify, document and assess changes that may impact compliance with GDP. Such changes may include, for example: a change in an insulated shipper used to transport cold chain medicinal products, a change in the settings of a heating system, or the relocation of a medicinal product storage area within a warehouse. Such changes may have a significant GDP impact and may have the potential to affect the quality of medicinal products wholesaled. Therefore, it is vital that the change is conducted in a controlled manner.

A change control procedure and associated form should be implemented. Its purpose should be to ensure that all changes to the operation are fully evaluated in terms of impact on product quality and traceability. The evaluation process should identify the areas impacted by the change, including processes, equipment, personnel, training, validation, quality system and regulatory

implications. The required actions to give full effect to the change and ensure its implementation should be identified and assigned to relevant personnel. In addition, changes should be formally approved by the relevant managerial representative of the areas of the operation impacted by the change and also by the responsible person (RP) prior to implementation. Changes should also be subjected to periodic review to ensure completion of actions which had been identified as required during the change control process. The principles of quality risk management should be built into the change control process. Each change should be considered and a decision taken as to whether a risk assessment is required prior to approval of the change for implementation. The requirement for a risk assessment to be considered should be documented on the change control form.

The role of management

The role of management within the wholesaling operation has been emphasised within the guidelines. It is imperative that management is involved, provides adequate resources and maintains oversight of GDP compliance.

Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It is a valuable component of an effective quality system. Risk management may be used to assess the risk posed to the product as a result of a deviation from normal practices or to justify a proposed deviation from accepted practice. The use of risk management should be based on scientific knowledge, reason and practices. The level of detail contained within the risk management process should be reflective of the level of risk to the product. Implications for product quality, security, traceability and follow up actions should be detailed. Risk assessments should be carried out by competent personnel and should be reviewed and approved by relevant personnel, including the RP.

Companies should have a procedure in place and training should be provided. All documentation for risk assessments performed should be available to an inspector during the course of an inspection.

For more information on risk management and performing risk assessments, consult the ICH Harmonised Tripartite Guideline entitled 'Quality Risk Management – Q9'. This document is available for download on the ICH website.

Deviations, investigations and corrective and preventive actions (CAPA)

Deviations are non-conformances with GDP, Regulations or in-house procedures. A procedure should be in place outlining the process for identifying, documenting, investigating and closing deviations and the timelines involved. The RP should be notified of deviations and an assessment should be performed to determine product quality implications and/or impact on the quality system.

It is important to note that wholesalers should commence the documentation of investigations immediately upon a potential deviation or incident being identified. Should the outcome of an investigation conclude that no deviation has occurred then the documentation of the investigation should still be maintained and available to an inspector. An example of this may be where an investigation is commenced into stock discrepancies identified during stock counts where the outcome of the investigation is the location of the missing stock.

Deviation investigations should aim to identify the root cause of the deviation. Corrective and preventive actions (CAPAs) may arise as a result of deviations, self-inspections, observations or from other incidents.

A log of deviations and suspected deviations should be maintained and all investigations, root cause identifications and resulting CAPAs documented. CAPAs should be subjected to regular review to ensure their full implementation and effectiveness.

The principles of quality risk management should be built into the deviation process. Each deviation should be considered and a decision taken as to whether a risk assessment is required. The requirement for a risk assessment to be considered should be documented on the deviation form.

CHAPTER 2 PERSONNEL

Responsible person

~~The wholesaler is~~Wholesalers are required to appoint a management representative to act in the role of 'responsible person' (RP). The RP is considered to be the key member of staff accountable for ensuring that the quality, safety and traceability of medicinal products is maintained within the supply chain.

The RP must ensure that the conditions of the WDA have been and are being complied with and that the GDP guidelines are being followed~~.~~ for the duration of time the individual is named on the authorisation as RP. A number of the GDP requirements may be delegated by the RP to other members of staff; however, they must personally:

- ensure that the quality system is implemented and maintained
- release returned products to saleable stock
- approve, sign and date all SOPs
- be involved in the approval of suppliers and customers

In addition, they should be involved in the process whereby any decision is made to quarantine or dispose of returned, rejected, recalled or falsified products. For returned medicinal products being disposed of, the RP need not approve each disposal but is required to maintain oversight of the process. The RP does, however, need to approve each return to saleable stock of a returned medicinal product. The marketing authorisation holder should be involved in the decision-making

process relating to recalls and suspected falsified medicinal products. The decision should be documented and recorded.

~~RPs should have sufficient pharmaceutical knowledge and experience to ensure full discharge of their responsibilities.~~ Wholesalers should have precise criteria for the selection of a suitable ~~candidates~~candidate(s) for undertaking the role of RP. This should take into account the complexity of the wholesale operation and the expertise and personal knowledge of the candidate. Key ~~considerations~~conditions in this regard are ~~knowledge and understanding of:~~: ~~the~~

1. Sufficient pharmaceutical knowledge and experience to ensure full discharge of their responsibilities. Curriculum vitae for the role of RP should outline all experience of relevance to GDP of medicines. Evidence of six months full-time direct GDP experience is considered a minimum requirement however all applications will be assessed on a case-by-case basis using a risk-based approach.

2. Knowledge, understanding and experience of:
   - The conditions of the WDA for which they are nominated.
   - ~~the~~The products wholesaled under the authorisation and the conditions necessary for their safe storage and distribution.
   - ~~relevant~~Relevant provisions of the Directives, Acts and Regulations pertaining to the wholesaling of medicinal products.

~~The HPRA assesses the suitability of the proposed RP as part of the assessment of an application for a WDA or application to vary an authorisation to add an RP. The suitability of the RP will also be assessed during inspection.~~

RPs who are not employed on a full-time basis at the authorised site may be considered eligible if they can meet the key conditions outlined above and can demonstrate:
- They are continuously contactable and available to attend the site as required.
- They will be present at the authorised site for an adequate amount of time to effectively carry out their duties. This must be risk based and justified.
- They are able to maintain oversight of their responsibilities during the periods of absence from the site.

The HPRA assesses the suitability of the proposed RP as part of the assessment of an application for a WDA or application to vary an authorisation to add an RP. The suitability of the RP will also be assessed during inspection. The outcome of this assessment may result in wholesalers having to address gaps in the knowledge or expertise of the candidate through training or other measures. All applications will be assessed on a case-by-case basis using a risk-based approach. Where the outcome is that the proposed RP is not considered suitable, selection of an alternative candidate may be required.

If, for any reason, an RP can no longer meet the obligations of the role of RP for the wholesaler, or should their contract cease, the wholesaler must submit an application to vary the authorisation

to remove the RP without delay. This application should propose a suitable replacement, be they an existing Deputy Responsible Person (DRP) that will change in role to RP or an alternative candidate. The named RP will be considered responsible for the wholesaling site until the suitable replacement has taken over responsibility.

Outsourced ~~RP~~responsible person

Wholesalers outsourcing the role of ~~the~~a RP ~~to a contract RP~~/DRP must have in place a contract ~~in place in order~~ to define, agree and control the activity. The ~~outsourced~~contract RP must fulfil all the responsibilities of the RP as per Paragraph 2.2 of the EU GDP guidelines (2013/C 343/01) and be given the authority to make decisions with regard to these responsibilities. In cases where the contract RP is not a signatory for activities impacting GDP, there must be a system in place to demonstrate that the ~~contracted RP has oversight of this approval.~~ contract RP has oversight of this approval. In the event that the contract personnel ceases their working relationship with the authorisation holder, contingencies for the handover of responsibilities should also be clearly outlined in the contract.

The time allocated for the ~~contracted RP~~contract personnel to perform their role at the authorised site should be based on a documented risk assessment that demonstrates the time is adequate to enable the contract RP/DRP to execute their responsibilities effectively. A record of the time spent operating in the role of RP should be maintained. The address of the ~~outsourced~~contract RP is required to be provided to the HPRA.

If an employee of one company is acting as RP on the WDA of another company within the same group of companies, there should be a contract or procedure in place documenting their duties and responsibilities as RP.

If a wholesaler employs the services of a contract RP, evidence may be requested of significant full-time experience of relevance to GDP of medicines predating their role as a contract RP. When this information is not readily available from a submitted application or from the company, the HPRA may engage in correspondence with the contract RP directly to seek additional information in relation to suitability and/or ongoing consultancy activities.

All applications will be assessed on a case-by-case basis using a risk-based approach. Where the outcome is that the proposed contract RP is not considered suitable, selection of an alternative candidate may be required.

Deputy responsible person

A deputy responsible person may be appointed. The function of this role should be to fulfil the duties of the RP in the event of their absence or where there is appropriate justification for delegation of activities as set out below.

Under appropriately controlled situations, duties required to be performed by the RP may be delegated to the deputy RP; this may be necessary in more complex or larger wholesale operations where it is not feasible for the RP to personally perform all of their duties in person. Formalised arrangements should be in place and the RP should still maintain oversight of the quality management system and be kept informed of key issues impacting on the quality system and medicinal product quality or traceability. Documented procedures should be in place outlining the delegation of responsibilities and records maintained to ensure that functions are appropriately discharged. The deputy RP should be named on the WDA in these cases.

The same requirements with regards to training and experience should apply to the deputy RP as to the RP. A role profile should be in place detailing the breakdown of duties between the two functions. There should be provisions in place to ensure effective handover of information between the RP and deputy RP when assuming or resuming duties.

CHAPTER 3 PREMISES AND EQUIPMENT

No guidance text is necessary for this chapter.

CHAPTER 4 DOCUMENTATION

Documentation

Distribution of documents to staff should be controlled in a manner such that only up to date documents are available in relevant areas and obsolete copies should not be accessible. This may be achieved by maintaining a distribution list with records of procedures issued and retrieved, including the dates on which these activities took place. Superseded master copies of procedures should be maintained for a period of at least five years.

In order to ensure that procedures are maintained and are reflective of current GDP requirements, a periodic review should be performed. This review should be documented and any recommendations should be implemented.

It is particularly important that SOPs relating to activities in certain areas (e.g. receipt of material at the goods inwards area) are available to staff in the relevant area for reference as required.

SOPs should describe the different operations which may affect the quality of the products.

In addition to those specified in the guidelines, there should be procedures in place for:
- training
- documentation control
- approval of suppliers and customers
- order processing and deliveries
- waste management
- self-inspection

- change control
- management review
- quality risk management
- deviation management
- corrective and preventive actions

Other procedures may also include:
- verification of safety features
- decommissioning unique identifiers
- staff sales
- promotional samples and sales representatives
- technical agreements
- temperature mapping requirements
- use of brokers
- parallel importation
- exempt/unauthorised products
- controlled drug management
- management of the cold chain

Validation and qualification

The guidelines introduce the concepts of validation and qualification.

Within Section 1.1 it is stated that 'All critical steps of distribution processes and significant changes should be justified and where relevant validated'.

Validation of critical processes
The wholesaler should first of all identify the critical steps within the process. Such steps may include goods-in, storage, order processing and dispatch. The wholesaler may further subdivide these steps into the critical sub-steps involved in each individual process. For example, goods-in may be subdivided into receipt on-site, delivery checking and acceptance, placing of goods into the goods-in area, detailed checking of products, product acceptance/rejection and finally removal of goods to storage/picking/rejection area.

Once the wholesaler has identified the critical steps, a decision should be taken as to which steps require validation (or indeed, whether all steps require validation). A risk management approach should be applied. Risks may be calculated by identifying the event which may occur and then assessing the probability of occurrence, severity of occurrence and the degree of detection of the event. In order to validate a process, the wholesaler should first of all clearly describe/map the process (including the use of diagrams/flowcharts where relevant). Each individual step within the process should then be tested to verify if it is achieving its desired effects and operating correctly. This may include the following:
- Does the process as described within the procedure comply with GDP?
- Are the required actions being carried out as per the procedure?

- Are there any additional actions being conducted that are not in the procedure?
- Do the records (either paper or electronic) capture the data required by the procedure?
- Are personnel trained on the process?
- Are there delegated personnel to conduct the activity in the event of absence?
- Is the equipment used for the process calibrated, maintained and operational?
- Is the correct equipment being used?
- Does each individual step allow the following step to proceed correctly?
- What could go wrong with the process and are there plans in place to provide for such eventualities?

Validation of processes should include an entire run through of a system from start to completion to ensure that each individual process does not have a negative impact on the following process.

Process validation should be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation).

Further relevant information is available on the European Commission website, in Annex 15 (Qualification and validation) of 'The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use'.

Computer validation

Before a computerised system (relating to GDP processes) is brought into use, it should be demonstrated, through appropriate validation or verification studies, that the system is capable of achieving the desired results accurately, consistently and reproducibly. The level of validation required will depend on the complexity of the system; whether it is a bespoke or 'off-the-shelf' system; and the level of customisation performed on the system. The wholesaler should examine its systems and decide on the level of validation required using a risk management approach. There should be documentation available describing the computerised systems in use and the level of validation performed or planned to be performed (for systems in place prior to the implementation of the guidelines).

Further information is available on the European Commission website, in Annex 11 (Computerised Systems) of 'The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use'.

Equipment qualification

The guidelines describe qualification as the action of proving that any equipment works correctly and actually leads to the expected results.

In order to qualify a piece of equipment, a written protocol should be generated outlining how the qualification will be conducted. The protocol should describe the piece of equipment along with its critical functions and attributes. The protocol should describe how the correct operation

of these critical functions and attributes will be verified along with acceptance criteria. The protocol should be reviewed and approved by the RP.

Following completion of the qualification exercise a report which cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies.

Further information is available on the European Commission website, in Annex 15 (Qualification and validation) of 'The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use'.

CHAPTER 5 OPERATIONS

Supplier approval

Prior to the purchase and receipt of any medicinal product, wholesalers must verify compliance of the supplying wholesale distributor or manufacturer with the principles and guidelines of good distribution practices. This includes (but may not be limited to) verifying whether the supplying wholesale distributor holds a WDA and a current GDP certificate or in the case of a manufacturer, a manufacturer's authorisation and a current GMP certificate.

The authority of the supplier to supply medicinal products must be established. It is the responsibility of the wholesaler to establish this and to obtain appropriate documentary evidence. In this regard, systems should be in place to ensure that each supplier is legally entitled to supply a particular medicinal product (i.e. the particular category of medicinal product being supplied, e.g. prescription-only medicine).

Checks may include requesting copies of wholesaler's or manufacturer's authorisations and associated GDP certificates, where available, or by consulting the list of authorised wholesalers/manufacturers published on the HPRA website for Irish suppliers or EudraGMDP for non-Irish suppliers; printouts should be obtained and retained as records of such checks. It is important to review the content and detail of each authorisation. Information on authorised wholesalers/manufacturers in Ireland is accessible on the HPRA's website (www.hpra.ie) and on the EudraGMDP database (www.eudragmdp.ema.europa.eu). If the original document is not in English, the company must ensure it is translated into English. It is expected that translations are carried out by an independent and certified translator.

When information cannot be independently verified using the EudraGMDP database or the local competent authority's website, another form of verification is required such as contacting the local competent authority directly. All communications related to this must be documented. Concerns relating to the legitimacy of wholesalers in other Member States may be referred to the HPRA by contacting compliance@hpra.ie.

If wholesalers become aware that a supplier does not hold a current GDP certificate, the wholesaler should confirm the reason with the supplier and should check that a certificate of non-compliance has not been issued on EudraGMDP. Wholesalers should also independently verify the reason and document any communication.

Periodic checks on existing suppliers should be performed to ensure that they maintain an authorised status and that changes in the sourcing arrangements are evaluated.

A robust system for approval of new medicinal product suppliers is a key component in the prevention of falsified medicinal products entering the supply chain. In addition to establishing the authority of the supplier, wholesalers should reasonably assure themselves that previous stages in the supply chain are considered to be sufficiently robust to ensure the legitimacy of the medicinal products concerned.

Wholesalers engaging the services of medicinal product brokers should verify that the broker is registered and should refer to Chapter 10 of the guidelines for further information on the GDP requirements relating to brokers.

Wholesalers sourcing medicinal products through brokers must ensure that such activities are carefully controlled and monitored. The wholesaler is ultimately responsible for ensuring the quality and safety of the medicinal products it sources and supplies onwards. The wholesaler should proactively assess previous stages in the supply chain and ensure the authorisation status of the actual supplier from which it receives the products.

The purchasing paperwork should also reflect the name and address of this supplier and not just the broker. Wholesalers should never allow their wholesale authorisation to be utilised by a third party.

The links between the quality and purchasing functions within the wholesale operation are particularly important. Given the criticality of procedures for approving new suppliers in ensuring the quality and safety of medicinal products handled by the wholesale operation, it is expected that the quality function maintain oversight of this process. In particular, the RP should be involved in the approval of new suppliers.

The system of supplier approval should be described in a procedure and all relevant steps in the process documented.

Wholesalers are requested to report to the HPRA issues which they consider suspicious or unusual with respect to the sourcing of medicinal products. Wholesalers may be assured that all such matters will be investigated confidentially. Information of this nature is an important component in the protection of the legitimate supply chain for medicinal products.

New product introduction

Wholesalers should have a procedure in place relating to the introduction of new products (be they medicinal products or otherwise) to their inventory. This procedure should include a requirement to assess and document the regulatory system under which the product has been classified (e.g. medicinal product, medical device, food supplement, cosmetic, biocide, etc.). For medicinal products the particular category should also be documented (e.g. prescription-only medicine, traditional herbal medicinal product, controlled drug, etc.), along with the required storage conditions and any additional requirements relating to their distribution, e.g. exempt medicinal products. Wholesalers should consult with their suppliers with respect to the classification of new products. Documentation should be available for review relating to each new product introduction.

Sourcing of exempt medicinal products

Since the commencement of the Medicinal Products (Control of Placing on the Market) (Amendment) Regulations 2019 (S.I No. 218 of 2019) in May 2019, wholesalers can source exempt medicinal products (EMPs) directly from non-European Economic Area countries under their WDA. Before commencing this activity, wholesalers should check that they are correctly authorised to wholesale the medicinal product category of EMPs. Wholesalers are required to notify the procurement and/or receipt of EMPs to the HPRA EMP database. Further information on the HPRA's Notification System can be found in the 'Guide to The Notification System for Exempt Medicinal Products'.

In general, wholesalers will need to take physical receipt of EMPs received from third countries before supplying onwards in order to perform the necessary quality checks and ensure accurate notification to the HPRA EMP database. However, in justified circumstances, it is possible for wholesalers to procure an EMP from a third country and supply it onwards to a customer in Ireland, without taking physical receipt of the product. The circumstances where this supply model may be appropriate are cases where supply of the EMP is time sensitive, for example, if the product is short dated or if there is an exceptional urgent patient need. In these circumstances, the wholesaler retains the regulatory responsibility for the EMP supplied and is required to have an alternate means of verifying the details of the physical product supplied, to ensure the necessary quality checks are complete and notification to the HPRA EMP database is accurate. This may require the wholesaler to obtain detailed information from its supplier and logistics partner, and verify product details with its customer.

Receiving

There should be a system in place for ensuring that medicinal products received which are intended for supply to the Irish market are authorised for sale in Ireland. This may be conducted by checking for the presence of a marketing authorisation number (i.e. PA, PPA or EU number) and recording the check (there is no requirement to record the actual number). This check should be performed on a sample from each batch of each product received. Batch numbers and expiry dates should also be checked at this stage to ensure that expired product is not supplied. These checks should be recorded. Medicinal products being supplied under the exempt medicinal

product (EMP) scheme should be checked upon receipt to verify that the products are as ordered in relation to the source market, manufacturer, strength and dosage form. Medicinal products received for the purposes of supply to customers based outside of Ireland should also be checked to ensure that they are as expected in relation to the marketing status of the product (e.g. bearing a PL number for supply to the United Kingdom).

The process for handling ~~of~~ non-conforming goods at goods-in should be described in a procedure and should include where the product is stored, what documentation is completed and how the stock is controlled on the warehouse management system (if applicable).

At the goods-in stage, it should be verified that all goods have been received from an approved supplier. To ensure this, goods-in personnel should have access to the list of suppliers approved under the company's quality system. Alternatively, an inventory management system may be used which permits medicinal products to be booked onto the inventory system only if the supplier is approved to supply that medicinal product.

Specific checks should be performed on products requiring refrigerated storage. These checks should include, but are not limited to, checking that cold chain conditions were maintained during transportation; and checking that the consignment(s) were received within the validated transportation time if received in qualified cold-chain shippers.

For products which require Official Control Authority Batch Release (OCABR), checks should also include checking for the presence of an Official Control Authority Batch Release certificate (see also Appendix 1, section 5 on OCABR).

If product is received under quarantine status, there should be systems and procedures in place to ensure that it is not released into saleable stock until all necessary conditions, including formal release, have been met. (Please note that this does not imply that wholesalers may receive product that has not been released for sale by a Qualified Person; receiving such products would require a wholesaler to be a named contract storage site on the manufacturer's authorisation of the manufacturer from whom they receive the products.)

It is the responsibility of primary distributors of medicinal products to ensure that the product has been released for sale on the Irish market. A control report or other documentary evidence (such as a declaration from the Qualified Person relating to the marketing status of that batch) should be obtained from the supplier or manufacturer with each incoming batch of medicinal product (received from another EU Member State). The requirement for the marketing authorisation holder, manufacturer or supplier to provide the control report or other documentary evidence should be formally included in any distribution agreement.

Article 51 of Directive 2001/83/EC sets out the basis for the control report, which is a document verifying that each batch of medicinal product has been manufactured and checked to be in compliance with both ~~Good Manufacturing Practices (~~GMP~~)~~ and its marketing authorisation. A control report should be signed by the Qualified Person responsible for batch certification. During

an inspection, a HPRA inspector may, in relation to any batch of a medicinal product which a wholesaler has received directly from another Member State of the EEA, ask to see the control report or other documentation verifying that the above compliance checks have been performed.

Records should be available of all checks performed at receipt and these should be available to the HPRA during an inspection.

Verification of safety features

In accordance with Commission Delegated Regulation (EU) 2016/161, prescription-only medicinal products and medicinal products not subject to a prescription but listed in Annex II of the ~~regulation~~Regulation can only be QP certified from 9 February 2019 onwards if they bear the safety features on their packaging, unless exempt in Annex II of the Regulation. Wholesalers are required to verify the safety features on medicinal products received from suppliers that are not a) the manufacturer of the product nor b) the MAH for the product (via their wholesale authorisation) nor c) the wholesaler designated by the MAH. A wholesaler can only act as the designated wholesaler if the designation is included in a written contract with the MA holder and this is reflected in the repository system. The verification of safety features can be completed at any stage between receipt and dispatch of the medicinal product and the process should be described in the company's quality system. In order to verify the safety features of a medicinal product, wholesalers should check both the authenticity of the unique identifier and the integrity of the anti-tampering device. The unique identifier is verified by scanning the 2D barcode on the product packaging into the repository system. The national repository system is managed by the Irish Medicines Verification Organisation (IMVO) (www.imvo.ie). The unique identifier is considered authentic when the repository contains an active unique identifier with a product code and a serial number that are identical to those being verified. The unique identifier is not considered authentic if it is not active on the repository system. The anti-tampering device is verified by physical examination and any signs of tampering with the tamper proof seal deems the product unsuitable for onward supply. During the initial period of operation, the system will be considered to be in 'use and learn' phase.

Therefore, wholesalers, pharmacies and hospitals should scan medicines bearing the safety features and if an alert or any other unexpected message is flagged, should continue to supply packs to patients in accordance with their existing procedures, unless they have overriding concerns that a falsified medicine is involved. Notwithstanding the above, if a pharmacist or wholesaler has reason to believe that packaging has been interfered with, based on their examination of the anti-tampering device on the pack, they must report their concern to the HPRA (as a suspected quality defect via the usual reporting mechanisms) and not supply the pack.

Derogations from the requirements described above are described in Article 21 of Commission Delegated Regulation (EU) 2016/161. These include cases where the medicinal products remain

within the physical possession of a single wholesaler but change ownership and where medicinal products are distributed within Ireland between two warehouses belonging to the same wholesaler or the same legal entity and no sale takes place.

Storage

Medicinal products should be kept separate from other goods. Storage conditions are normally specified on the containers, for example 'Keep the container in the outer carton', 'Keep the container tightly closed', 'Store between 2 and 8°C', or 'Do not store above 25°C'. Products must be stored in accordance with the labelled conditions.

Where there are no specified storage conditions, the products may be stored at temperatures not exceeding 30°C.

An initial temperature mapping exercise of the storage area must be performed and documented for areas greater than a few square metres. For areas less than a few square metres which are at room temperature, a risk assessment of the storage area can be conducted instead of a full mapping study. In order to ensure that the appropriate conditions are maintained, continuous temperature monitoring probes should be located according to the results of the mapping exercise or risk assessment. This applies to all areas where medicinal products are stored (e.g. bulk storage, pick-face, quarantine and returns areas). At a minimum, a max/min type thermometer should be used. The maximum and minimum temperatures should be recorded every day and the thermometer reset after the readings have been taken.

Temperature monitoring records should be reviewed and approved regularly to ensure compliance with the required storage conditions. Temperature excursions should be investigated immediately and documented. The manufacturer of the product should be consulted to ascertain the effect of any excursions from the labelled storage conditions. The method for investigating excursions should be described in a procedure.

Calibration certificates for temperature monitoring devices should be reviewed by the wholesaler to ensure that the accuracy of the devices is acceptable. Documentation should be available for inspection demonstrating that this review has occurred.

Temperatures should also be monitored during periods when temperature-measuring devices used routinely are being recalibrated. This may mean that auxiliary temperature measuring devices are required. These devices should also be calibrated.

For detailed information on temperature monitoring and mapping requirements refer to the HPRA document entitled 'Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances' (please see the 'Publications and Forms' section of www.hpra.ie).

Quarantined stock should be kept separate from approved stock. There should be a system in place to ensure that quarantined stock is not available for picking or returned to saleable stock inadvertently. An inventory of all quarantined product should be maintained and should include details such as date quarantined, batch numbers, expiry dates, quantities, reason for quarantining, disposition and date removed. This inventory may be maintained on a warehouse management system.

Care should be exercised by the wholesaler to ensure that they remain compliant with the guidelines in relation to situations where segregation using only a validated computerised system is not sufficient, such as falsified medicinal products, expired products, recalled products or rejected products.

Where a contract wholesale distribution site is listed on Annex II of the wholesale distribution authorisation, it is the responsibility of the wholesaler to ensure the contract wholesale distribution site is entitled to hold the particular categories of medicinal products. The wholesaler must obtain appropriate documentary evidence to substantiate this.

Pest control

A pest control programme should be in place. At a minimum this should include rodent control. Further controls may be required for birds, and flying and crawling insects; and may include electrical fly killers, glue traps, etc. Rodent control should cover both internal and external locations.

The programme should be described in a procedure. A bait map should show the locations of all pest control monitoring stations and should be approved by the wholesaler.

Any recommendations made by a pest control service provider should be completed and recorded. If recommendations are not completed, an explanation should be recorded. All pest control records should be approved by the wholesaler and maintained.

Establishment of the authority of customers to receive medicinal products

It is the responsibility of the wholesaler to ensure the entitlement of customers to receive medicinal products and to obtain appropriate documentary evidence to substantiate this. The approval system should ensure that each customer is not only legally entitled to receive medicinal products but also that the customer is authorised to receive the particular category of medicinal product that has been ordered. (For example, in the case of general sale retail customers, the system should ensure that medicinal products which are confined to pharmacy sale and/or prescription-only are not supplied.)
The links between the wholesale premises and the sales department are particularly important. The RP should be involved in the approval of new customers.

For wholesale customers the authority to receive medicinal products may be established by obtaining a copy of their WDA and by checking the authorised wholesale operations and the classification of medicinal products authorised. Wholesalers should also ensure that wholesale customers comply with the principles and guidelines of GDP, for example by checking for a GDP certificate. Ongoing periodic checks should be performed to verify the continued authority of wholesalers to receive particular categories of medicinal products. If the original documentation is not in English, the company must ensure it is translated into English. It is expected that translations are carried out by an independent and certified translator.

Wholesalers should independently verify the information provided by a customer in relation to their qualification. The HPRA maintains a listing of currently authorised Irish wholesalers on www.hpra.ie. This list may be used to check the current authorisation status of wholesalers and the category of medicinal products included within the scope of their authorisations. A record of all checks should be maintained. The European Community database, EudraGMDP may also be used in this regard and includes the authorised wholesale operation, on www.eudragmdp.ema.europa.eu. (Please note that, for security reasons, if a wholesaler is authorised to wholesale medicinal products covered by the Misuse of Drugs Act, this will not be detailed on the HPRA or EudraGMDP websites.) When information cannot be independently verified using the EudraGMDP database or the local competent authority's website another method of verification, such as contacting the local competent authority directly, is required, and all communication related to this must be documented.

There are various methods of qualifying customers which include (but are not limited to):
- requesting a copy of the WDA and GDP certificate
- for a pharmacy, verifying the registration as a retail pharmacy business
- checking the registration of healthcare professionals with the appropriate body, etc., and obtaining assurances that the products will be consigned to them at the proposed delivery address

More complex examples include verifying the bona fide where product is to be supplied to smaller hospitals without pharmacies, private clinics, nursing homes, health centres, charities, non-governmental organisations (NGOs), businesses and other entities who may be putting in place flu pandemic contingency plans, etc. In each of these cases, a registered medical practitioner should be engaged to act in a professional capacity for treatment of patients and the product should be consigned to them. A wholesaler supplying these customers should ensure that there is a practitioner acting in this capacity who will take responsibility to ensure that the medicinal product is received, stored, properly accounted for, and used in accordance with legislation.

The bona fide checks may include:
- establishing that the practitioner concerned is registered in the State
- checking that medicinal products are ordered by the practitioner and the relevant paperwork is approved by them personally
- obtaining a declaration, signed by the practitioner, verifying that they will ensure that the products will be stored and supplied in compliance with legislative requirements

Another common example includes universities and other similar research institutions carrying out non-invasive research and development. A wholesaler may supply medicinal products to these institutions where it has been established that the product is being used for research purposes which do not involve administration to either humans or animals. A wholesaler supplying medicinal products to these entities should obtain a personally signed, written declaration from the head of the academic institution or relevant department, confirming that the medicinal products concerned will be used for research purposes only and will not be administered to humans or animals. Products supplied to these entities should be clearly marked by the wholesaler to denote 'use for research purposes only and not for administration to humans or animals'.

For details on supplying medicinal products to first aid kit retailers refer to the HPRA document entitled 'Guide for Suppliers of First Aid Kits, Containing Medicinal Products, Supplying solely to the End-User' (please see the 'Publications and Forms' section of www.hpra.ie).

Supply of medicinal products to general sale retail customers should be controlled to ensure that supply is confined solely to medicines which are classified in Ireland as 'general sale'. A list of products which may be sold in such outlets is available on the HPRA's website.

Particular care should be taken in the evaluation of supermarket chains using centralised warehousing, to ensure they are operating on a basis which is exempted from the requirement for a WDA. Checks that the wholesaler should perform and document include the following:

- Are medicinal products supplied from the chain's centralised warehouse/distribution entity only to retail outlets that are part of the same company? The distribution centre and the retail outlet(s) must be owned and operated by the same registered company with the same registered address and company's registration office number. For a chain to remain exempt from requiring a WDA, medicinal products may not be supplied to another retail outlet outside of this company.
- Are the retail outlets supplied by the chain's warehousing entity operating on the basis of a franchise arrangement? If the retail outlets operate (to any extent) on a franchise basis, this is considered wholesaling on the part of the chain, in that parties outside of the company are being supplied.

Requirements for wholesale transactions for retail pharmacy businesses that also hold wholesale distribution authorisations

Companies/persons which operate both an authorised wholesaling business and a retail pharmacy business (RPB) from the same premises must ensure that the procurement and onward supply of medicines under the WDA is entirely separate from the procurement and supply activities of the RPB acting in its capacity as a dispensing pharmacy regulated by the Pharmaceutical Society of Ireland. The wholesaler is required to establish a separate account, or an equivalent supply arrangement, with its supplier(s) of medicines, which is distinct from its RPB account(s).

A supplying wholesaler is also legally required to ensure for its customers operating an authorised wholesaling business and a retail pharmacy business with a WDA from the same premises that an account, or equivalent supply arrangement, is established for wholesale transactions that is entirely separate from the account via which medicines are sold or supplied to that retail pharmacy business.

Decommissioning of unique identifiers prior to supply

The Commission Delegated Regulation (EU) 2016/161 defines 'decommissioning of a unique identifier' as:
'the operation changing the active status of a unique identified stored in the repository systems referred to in Article 31 of this Regulation to a status impeding any further successful verification of the authenticity of that unique identifier.'

In general, decommissioning of unique identifiers should occur at the end of the supply chain where the medicinal product is supplied to the public, for example when a medicine is dispensed to a patient in a retail pharmacy business. Wholesalers are required to decommission unique identifiers in a limited set of circumstances where it is not possible at the point of supply or where the product is not supplied to the public. The circumstances where a wholesaler must decommission unique identifiers are detailed in (a) – (k) of Article 23 of the Regulation and are as follows:

a) Medicinal products that are intended for export outside the EEA
b) Returned medicinal products that cannot be returned to saleable stock
c) Rejected medicinal products intended for destruction
d) Medicinal products that are being supplied to persons authorised or entitled to supply medicinal products to the public who do not operate within a healthcare institution or within a pharmacy
e) Medicinal products samples requested by the HPRA
f) Medicinal products supplied to veterinarians and retailers of veterinary medicinal products
g) Medicinal products supplied to dental practitioners
h) Medicinal products supplied to optometrists and opticians
i) Medicinal products supplied to paramedics and emergency medical practitioners
j) Medicinal products supplied to armed forces, police and other governmental institutions maintaining stocks of medicinal products for the purposes of civil protection and disaster control
k) Medicinal products supplied to universities and other higher education establishments using medicinal products for the purposes of research and education, with the exceptions of healthcare institutions

l) Medicinal products supplied to prisons
m) Medicinal products supplied to schools
n) Medicinal products supplied to hospices
o) Medicinal products supplied to nursing homes

There is further clarification on the entities that are considered not to operate within a healthcare institution or within a pharmacy. The Commission Delegated Regulation (EU) 2016/161 defines a healthcare institution in Article 3 as: *'a hospital, in- or outpatient clinic or health centre'*.

National legislation will further define 'in-or outpatient clinics' and 'health centres' as follows:
'In or out-patient clinic' means an in or out-patient/day patient clinic under the management or control of a hospital;
'health centre' means a health centre under the management or control of a hospital.

In summary, this means that wholesalers will be required to verify and decommission medicines bearing safety features prior to the supply to persons authorised or entitled to supply medicinal products to the public who are NOT a hospital or an in or out-patient/day patient clinic or health centre under the management or control of a hospital, for example, GP surgeries. Hospitals and in or out-patient/day patient clinic and health centres under the management or control of a hospital are required to verify and decommission medicines themselves prior to dispensing/administration. In exceptional circumstances a customer listed in (a) – (k) of Article 23 of the Regulation may decommission the unique identifier itself and in these cases the wholesaler should be informed.

Documentation accompanying each supply

Documentation accompanying each supply of medicinal product should incorporate the following information:
- date
- name and pharmaceutical form of the medicinal product
- quantity supplied
- name and address of the supplier and of the consignee
- batch number for all wholesale to wholesale transactions
- batch number at least for products bearing the safety feature
- applicable transport and storage requirements (note: this detail may be supplied separate to delivery docket or invoice)

Product disposal

All products that are rejected in house, rejected when received as returns or recalled should, if instructed accordingly by the MAH, be destroyed in an appropriate and timely manner and in accordance with waste legislation. The decision to dispose of products should be documented and recorded. Where the MA holder requests the return of waste product, this should be documented accordingly when dispatching the product.

There should be an inventory of products placed into waste. Medicinal products should be decommissioned from the repository before being sent for destruction. Records and certificates of destruction should be maintained.

Service level agreements should be in place with third party contractors.

For disposal of controlled drugs additional requirements apply and guidance may be obtained by contacting the Controlled Drugs unit at the HPRA (controlleddrugs@hpra.ie). Wholesalers should ensure that the quantity of controlled drugs awaiting disposal at the site is kept to a minimum.

Staff sales

Due to the legal restrictions governing the manner in which medicinal products classified as either 'pharmacy-confined sale', or 'prescription-only' may be sold or supplied to the public, wholesalers may not sell either category of medicinal product directly to staff.

Where staff are permitted to purchase medicinal products a procedure should be in place describing allowances and controls. Only general sale medicinal products may be purchased. The system for management of such sales must also ensure that sales of products containing paracetamol are in compliance with the Medicinal Products (Prescription and Control of Supply) Regulations 2003. A system to track sales should be in place. A listing of general sale medicinal products is available on the HPRA's website.

Physicians' samples (free samples)

The Medicinal Products (Control of Advertising) Regulations 2007 permit supply of free samples of medicinal products under defined circumstances to persons qualified to prescribe such products. Samples of medicinal products that may be given to, or administered to, patients must be stored and transported by the wholesaler or manufacturer to the end customer (i.e. the physician) in accordance with GDP.

Where such samples are stored by an authorised wholesaler, it is expected that the wholesaler will have the relevant controls described within a procedure and be able to provide documented evidence of the quantities of samples supplied, and the names and addresses of the physicians supplied. The wholesaler, in conjunction with the MAH, should ensure that adequate records are maintained to permit the rapid recall of any batch, if required. Restrictions on the quantities and product categories/types of such samples which may be supplied are stated in the above Regulations.

It should be noted that, in accordance with the Regulations, certain categories of medicinal products including controlled drugs such as antidepressants, hypnotics, sedatives or tranquillisers may not be supplied as samples.

Sales representatives' samples

Sales representatives may handle promotional (i.e. free) samples of products, for example for demonstration purposes. Sales representatives may not hold or supply free samples of medicines unless there are systems in place to guarantee that those samples are not given to, or administered to, patients. This is because sales representatives will not hold a wholesaler's authorisation in their own name and therefore will not generally meet all of the GDP requirements that apply to the holding and supply of medicines intended for patients.

Where such samples are stored by an authorised wholesaler and supplied to sales representatives, it is expected that the wholesaler, in conjunction with the MAH, will have the relevant controls described within a procedure and be able to provide documented evidence of the quantities of free samples supplied to those sales representatives. The wholesaler should have systems in place to obtain written assurance from the sales representatives or the MAH that the physicians will be advised that those samples should not be given to, or administered to, patients.

The use of brokers by wholesalers

Directive 2001/83/EC defines the brokering of medicinal products as:
'All activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.'

All persons brokering medicinal products are required to be registered with the competent authority of the EU Member State in which they are based. Registered brokers are listed on a publicly accessible database register in each Member State. The register of brokers based within Ireland is also available on the HPRA website (www.hpra.ie).

Brokers must comply with a number of requirements set out within the Directive including the maintenance of a quality system, the maintenance of documentation relating to all transactions brokered, and compliance with GDP as described in Chapter 10 of the guidelines.

The Directive sets out specific provisions for wholesalers using the services of a broker. These include a requirement for wholesalers to ensure that any broker they use is registered and complies with the relevant GDP requirements.

The Directive does not include a provision for competent authorities to certify broker operations for compliance with GDP requirements. As such, wholesalers are required to verify the GDP compliance of any broker they use, through inspection of their quality system. Third party service providers may be engaged by wholesalers for the purpose of conducting these inspections. Wholesalers engaging third party service providers must apply appropriate control and oversight in relation to the service provided.

Further information on the registration requirements for brokers may be obtained in the 'Guide to Registration Requirements for Brokers of Medicinal Products in Ireland' which is available on the 'Publications and Forms' section at www.hpra.ie.

CHAPTER 6 COMPLAINTS, RETURNS, SUSPECTED FALSIFIED MEDICINAL PRODUCTS AND MEDICINAL PRODUCT RECALLS

Management of returned medicinal products

A medicinal product should be considered as a 'return' once it has left the premises of the supplying wholesaler and subsequently returned to that premises. This may include the following examples:

- where a wholesaler supplies a customer with the incorrect product which is subsequently returned
- where a customer returns a product to a wholesaler which they ordered in error
- where a product is received back to the premises of a wholesaler having never been received by the customer (e.g. because the customer's premises was closed)

Wholesalers should be extremely vigilant in their assessment of the suitability of returned medicinal products to be placed back into saleable stock. Once the returned product has been placed back into saleable stock it may not be possible to distinguish between the returned product and the remainder of the stock even if the batch number of the returned product was recorded. The wholesaler must be extremely confident that the quality of the product has not been affected in any way whilst the product has been out of their care.

When a return is received back it should be placed in a separate area so that there is no risk that it would be returned to saleable stock prior to assessment in error. This separate area should be clearly segregated from saleable stock (either by physical means or by a validated computerised system).

All stages of the returns process should be documented. This documentation should allow all stages of the returns process to be traced including the person conducting each stage/activity. Should a wholesaler use a computerised system to control the returns process then the system should be validated as per section 3.3.1 of the guidelines.

A suitably competent person should perform the checks on returned products. This assessment should ensure compliance with the conditions referred to in section 6.3 of the guidelines.

Wholesalers must verify the safety features (i.e. the unique identifier and the anti-tampering device) for all returned medicinal products. If the verification of either of the safety features results in suspicion over the authenticity of a product it should be immediately quarantined. The HPRA should be contacted and an investigation into the issue conducted.

Wholesalers should pay particular attention to the time period elapsed since the product was dispatched. Products returned from a customer who does not hold a WDA or an MIA should only be considered for return to saleable stock if they have been received back into the wholesaler's care within 10 days from dispatch of the medicinal product from the wholesale site. As outlined above, returns of medicinal products are deemed to be appropriate where an incorrect order has occurred or in the instance of an incorrect or failed delivery. In these instances, it is envisaged that the product would be returned within the 10-day timeframe.

There may be some exceptional circumstances whereby a medicinal product is returned outside this timeframe. This may occur, for example, where a small number of packs of a medicinal product has been ordered to meet the anticipated needs of an individual patient to ensure continuity of treatment but that patient's medication is suddenly changed or is no longer required. Where such deviations to the 10-day timeframe occur, a risk assessment should be performed and a justification fully documented prior to considering the stock suitable to return to saleable stock.

Wholesalers should maintain separate documentation relating to any return placed back into saleable stock outside of the 10-day timeframe. A separate deviation should be raised for each exception. Wholesalers should be able to present information and supporting documentation relating to such exceptions to a HPRA inspector in a concise and consolidated manner.

The RP must approve returns to saleable stock. This approval should be documented and must occur prior to the product being placed back into saleable stock. For products returned to saleable stock outside of the 10-day timeframe, the RP should approve each exception individually by signing the relevant deviation form prior to the product being placed back into saleable stock. Such an approval should be in addition to their routine approval of the return to saleable stock of returned medicinal products.

If the product is to be rejected then it should be placed into a reject area.

Personnel involved in the returns process should receive appropriate training and should have sufficient experience in relation to the handling of products to increase their ability to identify falsified medicinal products.

The wholesaler must ensure that the correct storage conditions have been maintained during the period the product was outside of the wholesaler's control. There must be no reasonable possibility that the storage conditions have been compromised during this period.

If the wholesaler decommissioned the unique identifier of a product prior to dispatch, the decommissioned status may be reversed in order to avoid unnecessary waste prior to the product being placed back into saleable stock. In order to revert the decommissioned status the following conditions must be fulfilled:

- The wholesale site must have performed the decommissioning step.
- The reverting of the decommissioned status takes place no longer than 10 days after decommissioning.

- The medicinal products were not supplied to the public.
- The medicinal products have not expired.
- The products have not been registered on the repository system as being recalled, withdrawn, intended for destruction or stolen and the wholesaler had no reason to believe the product is not fit for resale.

Controlled drugs and products requiring storage at low temperatures

Special care must be exercised with the return of any products containing controlled drugs or products requiring storage at low temperatures.

Controlled drugs returned to wholesalers should immediately be identified upon receipt and placed into a secure storage location. The time period for which the product is outside of secure storage (e.g. during checking of the product) should be minimised.

Should a wholesaler decide to accept returns of products requiring storage at low temperatures the criteria for accepting these as described within the guidelines should be strictly adhered to and clearly described within a procedure. These criteria are also described within the HPRA guidance document entitled 'Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances' which is available in the 'Publications and Forms' section at www.hpra.ie.

The wholesaler must have documented evidence available for review confirming that the product was maintained within the cold chain for the entire time period during which it was outside of its control.

There should be a register or log of returns in place which should include all product details and reasons for return. The assessment performed on returned product should be documented and should include the final disposition. In line with the requirements of the guidelines, the RP must formally approve the release of returned medicinal products to saleable stock.

Wholesalers should be aware of the potential for falsified medicinal products to enter the supply chain through the returns process. All relevant staff members should be made aware of this.

Falsified medicinal products

It is imperative that all wholesalers operate using good governance and display vigilance in their efforts to prevent falsified medicinal products (as per definition in the guidelines) from being traded with other wholesalers or placed on the market.

Wholesalers must:

- Have a procedure in place detailing the processes to be followed in the event of identifying a suspected falsified product or of being notified that a (suspected) falsified product has been received.

- Be aware of the possibility of falsified medicinal products being supplied inadvertently through legitimate sources, i.e. other authorised wholesalers or returns from non-wholesale customers.
- Have robust systems for ensuring the legitimacy of their suppliers and ensure that these are regularly reviewed.
- Maintain a list of approved suppliers and ensure that products are only sourced directly from these approved suppliers. In this regard, it is imperative that the approval process includes assessment of the authority of the supplier to supply medicinal products.
- Be familiar with the history of the supply chain for products received and question previous stages in the supply chain, if deemed necessary.
- Train staff to be aware of falsified products and what to look out for.
- Ensure that the goods-in procedure involves a detailed inspection of products received which is capable of identifying changes or unusual aspects to the appearance and packaging of products.
- Treat any offer of lower-cost product with suspicion. Wholesalers should pay particular attention to offers of low-cost medicinal products. As such, wholesalers should be familiar with the market price of the medicinal products they source and normal fluctuations in this price. Offers below expected fluctuation should be treated cautiously and investigated to ensure these are genuine.
- Never allow their WDAs to be used by third parties to source or supply product.
- Be vigilant and do not allow themselves to be used by counterfeiters to 'launder' falsified product. If a single customer frequently buys or offers for sale suspiciously large quantities of the same product, no matter what the cost, then they may be acting in conjunction with the supplier of the product to pass falsified product through legitimate chains.
- Be aware of the possibility of falsified product entering the supply chain through returns.
- Be knowledgeable of products at risk of counterfeiting. Purchasers for the wholesaler should also be made aware of these products.
- Ensure that medicinal products bearing safety features are verified as genuine while in the wholesaler's care and are decommissioned before supply where appropriate.

A wholesaler in possession of a product that is found to be (or is suspected of being) falsified is responsible for the removal and quarantine of the product from saleable stock and for immediately informing the HPRA and the marketing authorisation holder. If suspicious that a product which is being offered or has been received is not genuine, then the HPRA and the marketing authorisation holder should be informed immediately. Received product which is suspected of being falsified should never be returned to the supplier without the consent of the HPRA.

Any suspicious approaches or activities noticed by a wholesaler should be reported to the HPRA without delay.

Recall

The wholesaler is obliged, in accordance with the Regulations and GDP guidelines, to have a recall procedure in place. This procedure must be submitted to the HPRA when making an application

for a WDA. This is to enable the swift and effective recall from the marketplace of defective and/or potentially harmful medicinal products. The HPRA should be included on the circulation list for any subsequent revisions of the procedure.

In the event of a recall, the responsibility of the wholesaler will depend on whether they act as a primary or secondary distributor of the product in question.

The recall procedure should include, at a minimum, the following:
- the role of the RP
- nominated responsibilities for coordination of the recall action
- 24hr contact numbers for the company (at least three personnel) and the HPRA
- requirement to discuss with the MA holder, primary wholesaler and agree any action with the HPRA before recall action is carried out
- the various classifications of a recall
- description of the batch traceability system and method of identification of product recipients within the distribution chain (inducing the details of any standard documents or software packages that record such information)
- method of handling recalled medicinal product
- arrangements to ensure segregation of recalled medicinal products from saleable product
- arrangements for return of recalled medicinal product to the MA holder or for destruction
- investigation and reconciliation report to be sent to the MA holder for primary wholesalers
- procedure to be followed in the event of a quality defect being discovered on-site

There should be an efficient and effective method for identifying customers supplied with a product subject to a recall along with templates of forms and letters for the execution of a recall.

The recall procedure should be regularly challenged (at least once per year) to ensure that the process is effective and capable of tracing all customers and products in the event of a recall in a timely manner. This challenge should take account of the complexity of wholesaler operations and should be carried out on a risk-basis. It may involve identifying a particularly complex batch of a product and reconciling quantities received with those in stock and distributed to customers. A challenge to the recall system need not be carried out where the company has participated in an actual recall during the previous year which has utilised the same traceability system. The effectiveness of all recalls (including recalls to challenge the system and actual recalls) should be evaluated after the recall has concluded. Where the review of effectiveness identifies gaps in the process, those gaps should be appropriately addressed in a timely manner and the recall procedure revised accordingly.

(For guidance refer to the HPRA document entitled 'Guide for Recall of Medicinal Products for Human and Veterinary Use' available on the 'Publications and Forms' section at www.hpra.ie).

CHAPTER 7 OUTSOURCED ACTIVITIES
CHAPTER 8 SELF-INSPECTIONS

No guidance text is necessary for these chapters.

CHAPTER 9 TRANSPORTATION

Transportation

Where contract service providers are used, the wholesaler must make itself aware of the operating procedures of that party (e.g. by audit). This assessment should include examination of the transportation methods and routes. The wholesaler should be fully aware of, and agree to, any operations subcontracted to another party by the contract service provider. The contracted arrangements for transportation should be documented in a service level agreement, and should include details of any sub-contracting.

The wholesaler must ensure that medicinal products are not subjected to prolonged periods of storage during transportation. It is the position of the HPRA that storage of medicinal products for periods longer than 48 hours during transportation (or for any storage of refrigerated product irrespective of the on-site storage time) would be defined as storage requiring that premises to hold a WDA.

For guidance on the transportation of medicinal products requiring storage at low temperatures refer to the HPRA document entitled 'Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances' available on the 'Publications and Forms' section at www.hpra.ie.

CHAPTER 10 SPECIFIC PROVISIONS FOR BROKERS

No guidance text is necessary for this chapter.

6 CONTACT DETAILS

For further information contact:

Compliance Department
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2,
D02 XP77

Telephone: +353 1 6764971
Fax: +353 1 6764061
Email: compliance@hpra.ie

APPENDIX 1 FURTHER GUIDANCE

1 Controlled drugs

Controlled drugs are those classified as such under the Misuse of Drugs Acts 1977 and 1984 and Misuse of Drugs Regulations 2017. Wholesale distributors supplying controlled drugs are required to hold an additional controlled drug licence/registration which permits the holder to store and supply these medicinal products. The HPRA is responsible for the administration of this licensing scheme, with the Department of Health retaining the role of formal signatory to the associated licences. This licence/registration requirement is in addition to the inclusion of controlled drugs as a category of medicinal product on the WDA.

Further information on the application process for a controlled drug licence/registration, including information on the safe custody requirements, may be obtained by contacting the Compliance department of the HPRA (compliance@hpra.ie or controlleddrugs@hpra.ie).

Wholesale distributors who submit an application for a controlled drug licence will be inspected by the HPRA for compliance with the requirements of the licence/registration and the Misuse of Drugs Regulations 2017 to ensure adequate controls are in place to maintain the security, reconciliation and accountability of those products.

For wholesalers distributing controlled drugs, procedures should be in place covering the following:

- licensing requirements including the application process for import and export licences (including endorsements) and annual licences
- cycle count checks including investigation and communication requirements when discrepancies are identified
- access and security restrictions
- annual and quarterly returns
- maintenance of registers (waste, quarantine, usage, etc.)
- requirements placed on wholesalers under the Misuse of Drugs Regulations, International Narcotics Control Board requirements and conditions of controlled drug licences/registrations
- theft/shortage including investigation and communication requirements
- certification of the controlled drug safe by An Garda Síochána

Wholesalers should ensure they keep themselves informed of legislative updates relating to controlled drugs, for example previously uncontrolled substances becoming controlled.

Wholesalers should also conduct a risk assessment on products wholesaled by them to identify products which, whilst not being classified as controlled drugs, are still at risk of diversion. Wholesalers are advised to increase the security and stock checking controls that they have in place for such products.

In accordance with the Misuse of Drugs Acts and Regulations, the wholesaler must maintain the security chain for controlled drugs from the point of receipt to the point of delivery to the customer.

There should be control systems in place for deliveries of these products. There should be a policy on transport selection and also a procedure on what to do in the event of theft; note this should include reporting to the HPRA.

If third party contractors are engaged, additional security controls should be considered, particularly with regard to the selection of courier companies.

The deliveries should be made directly to the pharmacist at the hospital or retail pharmacy, and appropriate documents signed on receipt and returned to the wholesaler providing proof of delivery.

2 Parallel importation and parallel distribution

Parallel importation is the importation from an EU Member State or a country within the EEA of a medicinal product which is equivalent to one already authorised for the Irish market, by an importer or wholesaler other than the importer or wholesaler appointed by the MAH of the product on the Irish market.

The HPRA operates two schemes for these products. Where the product to be imported differs in any respect from that on the Irish market, a parallel import licence (PPA) must be obtained before distribution of the product can commence. Where the product to be imported is identical in all respects (including identical packaging, labels and leaflets) to the product on the Irish market, a dual pack import registration (DPR) is required before the product is distributed in Ireland.

The HPRA has prepared a separate guideline entitled 'Guide to Parallel Imports - Human Medicines' which is available on the 'Publications and Forms' section at www.hpra.ie. This guideline will be of interest to both holders of parallel import licences and wholesalers distributing these products.

For parallel distribution of centrally authorised products, consult the Human Medicines section of the EMA website. Refer to: European Medicines Agency - Human Regulatory – Post-authorisation – Parallel distribution.

3 Procure and supply wholesalers

Not all wholesalers receive, handle or store the medicinal products that they procure and supply. This may be due to the physical storage being outsourced to another wholesaler, or to the physical route which the product takes going directly from the wholesaler's supplier to the wholesaler's customer. In all cases the wholesaler is still responsible for the quality of the

medicinal products which they supply. Technical or quality agreements should be in place between all entities involved in the supply chain. Procedures should outline methods for ensuring that the quality of medicinal products is maintained and how oversight of outsourced operations is managed. Wholesalers should be able to demonstrate compliance with all aspects of GDP relevant to their operation.

4 Wholesaling of exempt sourced medicinal products

In general, any medicinal product placed on the Irish market is required to be the subject of a valid product (marketing) authorisation granted by the HPRA in accordance with the Medicinal Products (Control of Placing on the Market) Regulations 2007. Certain other products are authorised centrally by the European Medicines Agency for marketing in all Member States and are the subject of European marketing authorisations granted under EU Regulation 726/2004.

There are some exemptions in the Medicinal Products (Control of Placing on the Market) Regulations 2007 from the requirement that each medicinal product be the subject of a marketing authorisation. Of relevance to wholesalers is Paragraph 2, Schedule 1 which states that:
'The provisions of paragraphs (1) and (2) of Regulation 6 shall not apply to the sale or supply of a medicinal product in response to a bona fide unsolicited order, formulated in accordance with the specifications of a practitioner for use by his individual patients on his direct personal responsibility, in order to fulfil the special needs of those patients, but such sale or supply shall be subject to the conditions specified in paragraph 3.'

There are a number of specific requirements with regard to these products which are detailed in Article 17 (2) of Schedule 2 of the Medicinal Products (Control of Wholesale Distribution) Regulations 2007, and also Paragraph 11 of the Medicinal Products (Control of Placing on the Market) Regulations 2007. Wholesalers should be aware of these requirements and should have the necessary documentation and systems in place.

Wholesalers distributing medicinal products exempted from the regulations must have the category 'Exempt Medicinal Products' approved on their authorisation.

(For detailed guidance, refer to the HPRA document entitled 'Guide to The Notification System for Exempt Medicinal Products' available on the 'Publications and Forms' section of www.hpra.ie.)

5 Official Control Authority Batch Release Certificate

Under Article 114 of Directive 2001/83/EC the competent authority of a Member State may require the holder of a marketing authorisation to submit samples from each batch of certain products for examination by a state laboratory, or a laboratory designated for that purpose, before release of the batch on to the market. If the laboratory is satisfied that the batch is of appropriate quality for marketing it issues an OCABR certificate for the batch.

This OCABR requirement may be applied only to certain categories of medicinal products including:

- live vaccines
- immunological medicinal products used in primary immunisation of infants or of other groups at risk
- immunological medicinal products used in public health immunisation programmes
- new immunological medicinal products or immunological medicinal products manufactured using new or altered technology or new for a particular manufacturer
- medicinal products derived from human blood or plasma

Any wholesaler receiving a batch of medicinal product covered by OCABR requirements from another Member State of the EEA should receive, along with the documentation for the batch, a copy of the OCABR certificate for the batch.

It is recommended that the requirement for the product authorisation holder or manufacturer to supply an OCABR certificate with each relevant batch be formally included in any distribution agreement.

A HPRA inspector may, during the course of an inspection, ask to see the OCABR certificate relating to any relevant batch, which that wholesaler has received directly from another Member State of the EEA.

The requirement for a wholesaler to have an OCABR certificate does not apply when:

- The wholesaler has been supplied by another Irish based wholesaler.
- The wholesaler has been supplied directly by an Irish based manufacturer.

There should be an effective procedure in place to ensure that product is not permitted to be sold prior to the OCABR certificate being received. A list of products requiring an OCABR should be maintained and available to all relevant staff (particularly goods-in staff). The member(s) of staff who may approve a batch for sale should be limited and documented. Those staff members should have the relevant training and expertise.