



**IRISH MEDICINES BOARD  
GUIDE TO WHOLESALING OF MEDICINAL PRODUCTS  
FOR HUMAN USE IN IRELAND**

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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 document is to provide guidance on the regulations covering the wholesale distribution of medicinal products for human use in Ireland.

The licensing authority for the wholesaling of medicinal products for veterinary use is the Department of Agriculture, Fisheries and Food ([www.agriculture.gov.ie](http://www.agriculture.gov.ie)) and therefore those products are not covered in this document.

## 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 and cognate words are construed accordingly. This 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). Wholesale and distribution of medicinal products are considered to be synonymous.

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 wholesaler’s authorisation, unless exempt under the Regulations, and must comply with the Regulations, Directives and guidelines discussed in this document.

The purpose of authorisation of wholesalers is to ensure that the standards of medicinal product quality, safety and traceability which exist within the manufacturing sector are also maintained within the distribution chain to the point where the hospital or retailer (pharmacy or general sale) takes possession of the product. The authorisation holder is obliged to adhere to certain legal and distribution practice requirements which ensure the maintenance of these standards.

This guidance document covers the wholesale distribution of medicinal products for human use and includes:

- A summary of the applicable legislation
- An overview of the EU Guideline on Good Distribution Practice, with which a wholesaler must comply in order to become authorised and to retain the authorisation
- Discussion of policy and IMB requirements relating to wholesale distribution of medicinal products for human use.

In Ireland, the majority of medicinal products supplied to patients are distributed through full-line pharmaceutical wholesalers. The full-line sector is structured into primary wholesale and secondary wholesale divisions. The roles played by each within the supply chain are very distinct. Primary wholesale is defined as the wholesaler which places a medicinal product on the market on behalf of the marketing authorisation holder (MAH). Primary wholesale generally operates on the basis of pre-wholesale, where batches of product for the market place are sourced from the marketing authorisation holder and supplied onwards to other wholesalers. In effect, the primary wholesaler is placing the product on the Irish market on behalf of the MAH. A secondary wholesaler sources product from either primary wholesale or other wholesalers and supplies it onwards to retailers.

The distribution sector of the pharmaceutical industry has undergone significant development over recent years. This development has seen the entry of many new types of operators into the supply chain. One of the largest areas of growth has been the provision of support services to the pharmaceutical industry including contracted storage and logistics. Other changes within the Irish market include the establishment of wholesale operations supplying parallel-imported products to the marketplace through the Parallel Product Authorisation (PPA) and Dual Pack Import Registration (DPR) schemes, along with parallel distribution of centrally authorised products. Some retail pharmacies have also extended their role within the supply chain and undertaken a limited range of wholesaling activities.

In addition to an expansion in range of wholesale operators acting in the marketplace, the range of activities performed by wholesalers has also increased in complexity including use of out-sourced and contracted services, distribution of medicinal products subject to increased regulatory requirements and participation in the distribution of medicinal products to markets outside of Ireland.

This guidance document discusses the legislative and good distribution practice requirements applicable to the wholesaling of medicinal products. In particular, the application of these requirements and the IMB's expectations in terms of ensuring the maintenance of medicinal product quality, safety and traceability are discussed in the context of the increased complexity in the supply chain.

### **3. LEGISLATIVE BASIS**

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

The Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (S.I. No. 538 of 2007) transpose the requirements of Title VII of Directive 2001/83 EC (as amended) into national legislation. In addition, these Regulations also consolidated and updated the requirements of previous legislation governing this area.

These Regulations were amended in 2009 and 2010 by the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2009 (S.I. No. 2 of 2009) and the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2010 (S.I. No. 286 of 2010), respectively. The 2009 amendment included measures to control the distribution of advanced therapy medicinal products, and permit the advertising of exempt medicinal products in certain prescribed circumstances. The 2010 amendment gives effect to Directive 2009/120/EC, which replaced Part IV (dealing with advanced therapy medicinal products) of Annex 1 of Directive 2001/83/EC, insofar as Part IV relates to control of the wholesale distribution of those products.

Together these Regulations may be cited as the Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended. For the purposes of this guideline these collectively will be hereinafter referred to as the ‘regulations’.

A summary of the requirements of the Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended, is included as Appendix 1 to this document.

The Irish Medicines Board (IMB) is designated as the Competent Authority in Ireland for the authorisation of wholesale distributors of medicinal products for human use under section 4(1) of the Irish Medicines Board Acts of 1995 and 2006.

Copies of the Acts and Regulations referred to throughout this document are available from the Government Publications Sales Office, Molesworth Street, Dublin 2 or may be viewed and downloaded from the Attorney General’s website, [www.irishstatutebook.ie](http://www.irishstatutebook.ie).

### **3.1 Distribution of controlled drugs**

Controlled drugs are those declared as such under the Misuse of Drugs Act 1977 and 1984. 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 IMB is responsible for the administration of this licensing scheme, with the Department of Health and Children 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 wholesaler’s authorisation.

Further information on the application process for a controlled drug licence/registration, including information on the safe custody requirements, can be obtained by contacting the Compliance department of the IMB ([compliance@imb.ie](mailto:compliance@imb.ie)).

Wholesale distributors making an application for a controlled drug licence will be inspected by the IMB for compliance with the requirements of the licence/registration and the Misuse of Drugs Regulations 1988, as amended, to ensure adequate controls are in place to maintain the security, reconciliation and accountability of those products.

### **3.2 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/wholesaler other than the importer(s)/wholesaler(s) appointed by the MAH of the product on the Irish market.

The IMB 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 IMB has prepared a separate guideline entitled '[Guide to Parallel Imports - Human Medicines](#)' which is available at [www.imb.ie](http://www.imb.ie). This guideline is of interest to both holders of parallel import licences and wholesalers distributing these products.

For parallel distribution of centrally authorised products, the Human Medicines section of the EMA website: [www.ema.europa.eu](http://www.ema.europa.eu) should be consulted. See link: [European Medicines Agency - Guidance - Parallel distribution: Regulatory and procedural guidance](#)

## **4. EXEMPTIONS FROM THE REQUIREMENT FOR A WHOLESALER'S AUTHORISATION**

- (i) If an authorised medicinal product is imported from a third country (i.e. outside the EU or European Economic Area (EEA)) the importer must hold a manufacturer's authorisation (not a wholesaler's authorisation). Hence the importer is required to comply with all the relevant provisions of a manufacturer's authorisation. Interested parties should contact the Compliance department of the IMB for further assistance on this issue.
- (ii) An import agent (i.e. carrier) of medicinal products, who does not own the products and acts solely as a carrier or import agent for medicinal products, generally does not require a wholesaler's authorisation provided the products are delivered to an authorised manufacturer for products imported from outside of the EEA or to an authorised wholesaler for products imported from within the EEA.

However, if an import agent holds medicinal product for any appreciable length of time (greater than 48 hours) an authorisation is required. For refrigerated product any storage at the premises of a carrier may be regarded as falling within wholesale authorisation requirements.

A wholesaler's authorisation is also required for a carrier (logistics service provider) who holds medicinal products at a storage location for greater than 48 hours (or for any storage of refrigerated product irrespective of the on-site storage time) regardless of where the product was supplied from.

- (iii) A registered pharmacy which sells or supplies a medicinal product in accordance with a registered doctor's or registered dentist's prescription does not require a wholesaler's authorisation.
- (iv) Retailers selling authorised medicinal products directly to the public do not require a wholesaler's authorisation. This includes individual retail outlets and, in certain circumstances, retail chains, which use centralised warehousing to coordinate the supply of medicinal product stock to individual retail outlets within the chain.

Where the retail chain obtains the medicinal product stock for supply to the public through its retail outlets, it does not require a wholesaler's authorisation. In these circumstances the supply of medicinal products from the supermarket chain's warehouse to each retail outlet is conducted within the company only and does not involve supply to any party outside of this. As such, the warehousing entity is not considered to be wholesaling and authorisation requirements are not applicable.

It is important to note that retail chains which use centralised warehousing but operate as franchised retail outlets are not exempt from wholesale authorisation requirements. The exemption applies where the company's legal entity, which includes the warehousing operation, is registered as a retailer.

- (v) The holder of a manufacturer's authorisation issued by the IMB does not require a wholesaler's authorisation if it only distributes products manufactured at the manufacturing site and all wholesaling activities are performed at the manufacturing site.

However, a manufacturer must hold a wholesaler's authorisation if it distributes any of its own medicinal products from a site other than the one at which manufacture takes place. An authorised manufacturer also requires a wholesaler's authorisation if involved in distribution of a medicinal product manufactured in its entirety by another manufacturer.

- (vi) A wholesaler's authorisation is not required for the sale by or under the personal supervision of a pharmacist in a dispensing pharmacy to a range of healthcare professionals as specified within the Regulations:
  - a) a registered medical practitioner,
  - b) a registered dentist,
  - c) a registered dispensing optician,
  - d) a registered optometrist,
  - e) a registered veterinary surgeon,
  - f) a person who is acting as a pre-hospital emergency care provider,
  - g) a person lawfully entitled to obtain medicinal products for administration to patients in the course of a business as a hospital.
- (vii) A wholesaler's authorisation issued by the IMB is not required for holders of a wholesaler's authorisation issued by the competent authority of another EEA Member State which distribute directly to their customers in Ireland from that other State.
- (viii) A wholesaler's authorisation is not required for the supply of an investigational medicinal product where the product is to be used in a clinical trial in accordance with Regulation 11 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 (S.I. No. 190 of 2004), as amended.

If there is any clarification required as to whether a particular activity is subject to wholesale regulatory requirements, advice may be sought from the IMB at [compliance@imb.ie](mailto:compliance@imb.ie).

## **5. EUROPEAN UNION GUIDELINES ON GOOD DISTRIBUTION PRACTICE**

Article 80(g) of Directive 2001/83/EC, as amended, refers to the requirement that wholesalers of medicinal products for human use must comply with the EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use. These guidelines (hereafter referred to as the GDP guidelines) are published separately and form the basis for the quality system to be maintained by wholesale distributors. Compliance with the GDP guidelines is the minimum requirement that a wholesaler must meet in order for a wholesaler's authorisation to be issued.

The requirement to comply with the GDP guidelines is also included within the Irish Regulations governing wholesale distribution of medicinal products and as a condition of the wholesale authorisation with which the holder must comply.

The full text of these guidelines is available at <http://ec.europa.eu/health/files/eudralex/vol-4/gdpguidelines1.pdf>

The GDP guidelines are structured into a number of sections which cover the necessary components of a quality system for wholesalers and include the following:

- Principle
- Quality Systems
- Personnel
- Documentation
- Premises and Equipment
- Deliveries to Customers
- Returns
- Self-Inspections

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

### **5.1 Quality Systems**

The wholesaler is required to have a quality system which is a documented set of procedures which describe, in sufficient detail, all the activities which could affect the quality of the medicinal products and the traceability system.

The objective of the quality system is to ensure that the quality and traceability of medicinal products is maintained while under the control of the wholesaler and that the requirements of legislation and GDP guidelines are met. The quality system also ensures consistency of approach in terms of ongoing operation and performance of the wholesaler. It should ensure that deviations and non-conformance are appropriately managed and investigated, including the identification of actions to prevent recurrence. In addition, the quality system should include appropriate mechanisms for the management of change.

The attainment of the quality objectives outlined above is considered the responsibility of senior management within the wholesale operation. The participation and commitment of all staff within the operation is required to ensure that the system is fully effective. The provision of a comprehensive training programme, which includes consistent focus on the quality system, is a key feature in this regard.

The entry of counterfeit medicinal products is one of the greatest threats to the legitimate supply chain. The implementation and consistent operation of an effective quality system should form the basis of a wholesaler's anti-counterfeit strategy.

The quality system should include policies, standard operating procedures (SOPs), and related forms. The effectiveness of the quality system in ensuring its objectives should be monitored and updates implemented as required.

The section on documentation describes the required format and content of SOPs in more detail.

In particular, the SOPs which form the basis of the quality system should:

- Ensure adequate documentation control
- Ensure that the implementation of change is effectively managed
- Ensure monitoring of the effectiveness of the quality system
- Ensure that all activities and procedures are fully defined to guarantee:
  - o that the quality and safety of medicinal products are maintained while under the control of the wholesaler,
  - o the provision of a system which can ensure full traceability of medicinal products received and supplied,
  - o that products are only received from persons authorised to supply them and are supplied only to persons entitled to receive them,
- Ensure that non-conformances and complaints are fully investigated.

See also sections on documentation (5.3) and procedures (5.3.1).

Modern wholesale operations involve increased use of contracted service providers and out-sourced support services. In line with this the quality system should also include technical and/or service level agreements and contracts which should ensure that the roles and responsibilities of all parties are fully defined and appropriately devolved. Examples of the types of contracted operations which should be considered are given below. These are not considered to be exhaustive and wholesalers should fully evaluate their use of contracted service providers to ensure that they are adequately defined and covered under their quality system.

If acting as a primary distributor there should be technical agreements in place with the marketing authorisation holder (MAH). These technical agreements should detail the GDP roles and responsibilities of both parties including details on transportation arrangements, the receipt of goods, customer approval, documentation, recalls, returns and customer complaints and training requirements (where applicable). 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 will be examined during the course of an IMB inspection.

Service level agreements should be in place with relevant third party service providers for those activities which may have an effect on the quality of medicinal products wholesaled or on the security of the supply chain. Such services may include (but are not limited to) transport providers, contract personnel (including contract responsible persons), contract storage, pest control providers, maintenance and calibration service providers, alarm monitoring service providers and pharmaceutical waste disposal contractors. Such agreements should include details on activities carried out, level of service and GDP guideline requirements such as handling of products, training and documentation requirements.

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 an 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 may be required.

## **5.2 Personnel**

### **5.2.1 Responsible Person**

The wholesaler is required to appoint a management representative in each distribution centre known as the '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 are maintained within the operation.

The RP must ensure that the conditions of the wholesaler's authorisation have been and are being complied with and that the GDP guidelines are being followed. A number of the GDP requirements can 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 counterfeit products. The marketing authorisation holder should be involved in the decision making process relating to recalls. The decision should be documented and recorded.

The RP should have sufficient pharmaceutical knowledge and experience to ensure full discharge of their responsibilities. Wholesalers should have precise criteria for selection of suitable candidates 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 in this regard are knowledge and understanding of:

- The conditions of the wholesaler's authorisation for which they are nominated.
- The products wholesaled under the authorisation and the conditions necessary for their safe storage and distribution.
- Relevant provisions of the Directives, Acts and Regulations pertaining to the wholesaling of medicinal products. Refer to Appendix 2.

The IMB assesses the suitability of the proposed RP as part of the assessment of an application for a wholesaler's authorisation 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. Where the outcome is that the RP is not considered suitable, selection of an alternative candidate may be required.

There should be an approved role profile in place defining the responsibility of the RP and should include the following duties, as a minimum:

- To ensure compliance with the general conditions of the authorisation.
- To ensure compliance with the requirements of GDP.
- To ensure that all aspects of the quality system are implemented and maintained.
- To approve, sign and date each SOP.
- To ensure that all relevant staff members are trained in the duties assigned to them.
- To review temperature records on a regular defined basis.
- To approve for return to saleable stock any medicinal product returned by a customer.
- To be involved in any decision to quarantine or dispose of returned, rejected, recalled or counterfeit products.
- To be involved in the approval of suppliers and customers.
- To fulfil their responsibilities personally.

#### 5.2.2 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 to allow this. However, 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 to define the delegation of responsibilities and records maintained to ensure that functions are appropriately discharged. The deputy RP should be named on the wholesaler's authorisation in these cases.

The same requirements with regards to training and experience should apply to the deputy RP as 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/resuming duties.

### 5.2.3 Training

Training is a key component of the quality system. Appropriate training should be provided for all staff members involved in the storage and distribution of medicinal products. The programme should be broad-based and include staff who may not generally be considered to have 'hands on' involvement, for example, staff involved in supplier and customer approval. Consideration should also be given to inclusion within the training programme of staff engaged through third party contract service providers, such as, delivery drivers and others as may be relevant.

Each employee should receive a general introduction to GDP and this should be supplemented by training relevant to their specific responsibilities, including training in appropriate SOPs.

A training plan should be in place describing the procedures and tasks which staff should be trained on. For all staff the plan should include training on a number of key procedures within the quality system irrespective of their areas of responsibility. This should encompass training on the procedures relating to the prevention of counterfeit medicinal products entering the supply chain and the strategy that would be adopted by the wholesaler in that eventuality. Training should also be provided to all staff on raising and reporting of non-conformances.

It is important that training plans are prepared at regular intervals so that the training objectives for individuals are defined and include timelines for completion. Training plans should also be reviewed regularly to ensure that objectives are achieved.

An assessment of the effectiveness of the training should be performed and described in a procedure. Before taking on any role, staff should have the appropriate ability and experience to ensure that they are capable of performing their duties. Wholesalers should ensure that employees of subcontractors who are involved in the storage or distribution of their products also receive training.

It should be ensured, on an ongoing basis, that all staff have adequate knowledge and expertise with regard to the activities performed by them. This may be assured by carrying out routine refresher training (including GDP) and/or performing routine assessments. All training events should be documented, ensuring that adequate details are recorded. Such details should include description of training procedure, document numbers and revision number trained on, date of training, duration and details of any assessment performed. All training records should be signed by the trainer and trainee and maintained for a minimum of five years.

### 5.3 Documentation

The wholesaler is required to have a documented quality system. Documents should be in the format of standard operating procedures (SOPs) and forms. A documentation control procedure should be in place detailing how procedures are version controlled and updated. A revision history should be available for all procedures recording changes made from the previous revision. A master copy of all documents should be maintained.

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 are not accessible to staff. This may be achieved by maintaining a distribution list which should record 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 arising from this 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) should be available to staff in the relevant area for reference when necessary.

#### 5.3.1 Procedures

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

In addition to those specified in the GDP guidelines, there should be procedures in place for:

- Training
- Documentation control
- Approval of suppliers and customers
- Order processing and deliveries
- Waste management
- Self-inspection
- Counterfeit product
- Change control

Other procedures may also include:

- Deviation management
- Staff sales
- Promotional samples and sales representatives
- Technical agreements
- Temperature mapping requirements
- Corrective and preventive actions
- Risk management
- Parallel importation
- Exempt/unauthorised products
- Controlled drug management

Procedures for various operations should be approved, signed and dated by the Responsible Person and the author.

A change control procedure should be put in place. 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 and the quality system. The necessary updates to give full effect to the change and ensure its implementation should be identified. In addition, changes should be formally approved by the relevant managerial representative(s) of the areas of the operation impacted by the change(s) prior to implementation. Changes should also be subjected to periodic review to ensure completion of the actions which had been identified as required during the change control process.

### 5.3.2 Records

Records should be made when each operation is taking place by the member of staff who performed the operation. Based on the records, the activities and events relating to the medicinal products should be traceable. Examples of records to be maintained include goods-in checks, temperature records, cleaning records, returns records and pest control reports.

All entries to GDP documentation should be legible and written in a manner to ensure against fading etc. Overwriting, use of ditto marks, correction fluids or pencil should not be allowed. All records should be signed and dated by the person carrying out the activity.

All records should be readily available during an inspection and retained for at least five years.

### 5.3.3 Supplier approval

The system of supplier approval should be described in a procedure.

Prior to purchase and receipt of any medicinal product, 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 should include requesting copies of wholesaler's or manufacturer's authorisations or by conducting the check against the list of authorised wholesalers on the IMB website and obtaining a printout. It is important to review the content and detail of each authorisation. Where the authorisation is presented in foreign language the wholesaler should request a copy in English. Wholesalers should also ensure the legitimacy of the authorisation. Information on authorised wholesalers in Ireland is accessible on the IMB's website ([www.imb.ie](http://www.imb.ie)). Concerns relating to the legitimacy of wholesalers in other member states can be referred to the IMB by contacting [compliance@imb.ie](mailto:compliance@imb.ie).

Periodic review of 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 of the wholesaler's anti-counterfeit strategy. In addition to establishing the authority of the supplier, wholesalers should also reassure themselves that previous stages in the supply chain are sufficiently robust to ensure the legitimacy of the medicinal products concerned.

Wholesalers sourcing medicinal products through third parties 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, insofar as is possible, 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 third party. 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 would maintain oversight of this process. In particular, the RP should be involved in the approval of new suppliers.

Wholesalers are urged to report, to the IMB, issues which they consider suspicious or unusual with respect to the sourcing of medicinal products. Such matters will be investigated confidentially. Information of this nature is an important component in protecting the legitimate supply chain for medicinal products.

#### **5.4 Premises and equipment**

The premises must be suitable and adequate to ensure proper storage and distribution of medicinal products.

##### **5.4.1 Receiving**

Receiving bays should protect deliveries and be separate from storage areas. Deliveries should be examined on receipt for damage and to ensure that the goods correspond to the order.

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 need 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 also be recorded.

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, there should be a method for goods-in personnel to access the list of suppliers approved under the company's quality system. Alternatively, an inventory management system may be used to ensure that medicinal products are only receipted onto the inventory system if the supplier is approved to supply that medicinal product.

Medicinal products requiring refrigerated and/or secure storage (e.g. controlled drugs) should be moved to their appropriate storage areas immediately following receipt and checking.

Specific checks should be performed on products requiring refrigerated storage. These checks should include, but are not limited to, checks on temperatures during transit, the time since packing at the suppliers versus validated transit time for cold-chain shippers.

For products which require Official Control Authority Batch Release (OCABR), checks should also include checking for the presence of a Controlled Authority Batch Release certificate (see also section 7 on CABR).

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.

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 verifying this 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 this should be formally included in any distribution agreement.

Article 51 of Directive 2001/83, as amended, 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, an IMB 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 IMB during an inspection.

#### 5.4.2 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 to 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.

Continuous temperature monitoring must be performed and documented in order to ensure that the appropriate conditions are maintained. 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.

Products should not be stored in close proximity to heating units and should not be stored directly on the floor to ensure proper air circulation and reduce the risk of incidental damage.

Storage of personal medication, food and drink should be prohibited in areas used for storage of medicinal products.

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 should be maintained of all quarantined product and should include details such as date quarantined, batch numbers, expiry dates, quantities, reason for quarantining, disposition and date removed. This inventory may also be maintained on a Warehouse Management System. The quarantine area should be segregated so that such product is separate from rejected stock.

Temperature monitoring records should be reviewed and approved regularly to ensure compliance with the required conditions. Any 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.

Temperature monitoring devices should be calibrated (i.e. certified that they are operating correctly and the certification should be traceable to a National Standard) to cover their operating range. Devices should be recalibrated as recommended by the manufacturer of the device or the calibration provider. Calibration certificates should be reviewed by the wholesaler.

Temperature should also be monitored during periods when the temperature measuring device that is used routinely is being recalibrated. This may mean that an auxiliary temperature measuring device is required. This device should also be calibrated.

Temperature mapping should be performed on all storage areas and cold rooms to ensure that all locations remain within the specified temperature limits over the year and to identify hot/cold spots. However, if the volume of medicinal products is limited to a small area and appropriate monitoring is in place, mapping may not be required.

Mapping should be performed during both summer and winter months. Mapping studies should be repeated after any significant changes to the warehouse temperature regulating equipment or layout. Protocols and reports should be available. Protocols should be approved by the wholesaler before the study commences and reports should be reviewed and approved afterwards. All probes used during mapping should be calibrated. The locations of routine monitoring probes should be based on worst-case locations identified during mapping.

For further detailed information on temperature monitoring and mapping requirements see the IMB document entitled '[Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances](#)' available at [www.imb.ie](http://www.imb.ie)

#### 5.4.3 Pest control

A pest control programme should be in place. At a minimum this should include rodent control. Further controls may be required for 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 devices and should be approved by the wholesaler.

If an third party service provider conducts the programme, a service level agreement should be in place detailing items such as the number of visits, level of follow-up, contacts and services provided. This agreement should be signed by both parties. Any recommendations made by a pest control provider should be completed and recorded. If recommendations are not completed, an explanation should be recorded detailing the reasons why. All pest control records should be approved by the wholesaler and maintained.

## 5.5 Deliveries to customers

### 5.5.1 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 may 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 medicinal products are not supplied.

For wholesale customers the authority to receive medicinal products may be established by obtaining a copy of their wholesaler's authorisation and also by checking the classification of medicinal products included. Ongoing checks should be performed to verify the continued authority of wholesalers to receive medicinal products and the category which they are entitled to receive. This is particularly important where the range of products supplied to a customer expands.

The IMB maintains a listing of currently authorised Irish wholesalers on [www.imb.ie](http://www.imb.ie). This may be used to check the current authorisation status of wholesalers and the category of medicinal products included within the scope of their authorisation. A record of all checks should be maintained. (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 IMB website).

There are various forms of customer bona fides checks of which simpler examples include (but are not limited to):

- requesting a copy of the wholesaler's authorisation;
- for a pharmacy, verifying the registration as a retail pharmacy business;
- checking the registration of healthcare professionals with the appropriate body etc.

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, businesses and other entities setting in place flu pandemic contingency plans etc. In each of these cases a registered medical practitioner(s) should be engaged to act in a professional capacity for treatment of patients and the product(s) 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 product is received, stored, properly accounted for, and used in accordance with legislation. The bona fide checks should 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 signed 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 in this manner should obtain a written declaration from the head of the academic institution or relevant department and personally signed by them, which confirms that the medicinal products concerned will be used for research purposes only and will not be administered to humans or animals. Products supplied in this manner 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 see the IMB document entitled '[Guide for Suppliers of First Aid Kits, Containing Medicinal Products, Supplying solely to the End-User](#)' available at [www.imb.ie](http://www.imb.ie).

General sale retail customers should also be evaluated to ensure these are appropriately authorised to receive medicinal products. Supply must be confined only to medicines which are classified in Ireland as 'general sale'. A list of products which can be sold in such outlets is available on the IMB's website see: [IMB General Sales List](#)

Particular care should be taken in the evaluation of supermarket chains using centralised warehousing, to ensure they are operating on a basis exempted from the requirement of a wholesaler's authorisation. 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 number. For a chain to remain exempt from requiring a wholesaler's authorisation, medicinal products cannot 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.

The links between the wholesale premises and the sales department are particularly important. The Responsible Person should be involved in the approval of new customers.

### 5.5.2 Documentation accompanying each supply

On the document accompanying each supply of medicinal product, the following information should be provided:

- Date
- Name and pharmaceutical form
- Quantity supplied
- The name and address of the supplier and of the consignee
- Batch number for wholesale to wholesale transactions

### 5.5.3 Transportation

The wholesaler should ensure that medicinal products are transported in such a way that:

- The identification is not lost.
- Contamination is avoided.
- Products are secure.
- Breakage and theft are avoided.
- Products are protected from inappropriate environmental conditions e.g. harsh weather.
- Delivery drivers (including contract drivers) are trained in GDP awareness.

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

### 5.5.4 Cold-chain

Products requiring refrigeration must be delivered in either refrigerated transportation vehicles or in insulated boxes. The RP must ensure that adequate delivery conditions are maintained for all deliveries.

The wholesaler must validate the worst case situation likely to be encountered during transport and ensure that the product does not come in direct contact with cool-packs (where applicable).

If cool-packs are in use, there should be a system in place to control their re-use and rotation to ensure that incompletely cooled packs are not used in error.

The process for packing and delivery of cold-chain product should be described in a written procedure and should replicate conditions used in the validation study. This procedure should also cover what is required in the event of unexpected occurrences such as van breakdown and cold-chain failure.

Careful consideration should be given to the format of the training and instruction given to staff on the management of medicinal products requiring cold storage during order assembly and dispatch. Staff should be assessed to ensure their competency in handling these operations and also procedures to be followed in the event of failure.

(For guidance refer to the IMB document entitled ‘[Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances](#)’ available at [www.imb.ie](http://www.imb.ie)).

#### 5.5.5 Controlled drugs

In accordance with the Misuse of Drugs Act and Regulations, the wholesaler must maintain the security chain for controlled drugs from the time of receipt to the time 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.

If using third party contractors, 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.

## 5.6 Returns

Medicinal product returns may only be accepted and returned to stock where these have been appropriately assessed and demonstrated as non-defective, as described in the EU GDP guidelines.

Documentation from the customer should be included with all returned products. This documentation should include details such as the invoice number and date of original supply, the product description, the quantity returned and a reason for the return. The wholesaler should only accept returns when this documentation is supplied at the time of the return.

Returns should be segregated from saleable stock until the decision relating to disposition of the stock has been formally made by the RP or deputy RP (See Section 3 for further guidance on the delegation of duties to a deputy Responsible Person) in accordance with the SOP for checking of returned products.

In accepting a returned product and assessing its suitability for release to saleable stock, it is important to consider if the return has been made by the customer within an acceptable timeframe. For the purposes of ensuring medicinal product traceability, wholesalers should only release product to saleable stock where it is ensured that the product was initially supplied by them to the customer.

The volume of returns that should be processed on a daily basis requires careful consideration. It is important this is managed so that a sufficient level of checking can be performed to ensure that only products of the appropriate quality are returned to saleable stock.

It is also important that staff assigned to work in the returns area, particularly those working on product quality assessment, have appropriate experience and training in this regard.

The returns procedure should describe the process for acceptance or refusal of returned stock.

The IMB position is that cold-chain products may only be returned to saleable stock where there is no reasonable possibility that the cold-chain has been compromised. For example, under the following circumstances, the return of product could be considered:

- The batch number of the distributed product is known, and:
- The entire process is validated (i.e. delivery to customer, opening of the packaging, examination of the product, returning of the product to the packaging and sealing of the packaging, collection by the courier/transporter, and return to the distribution site refrigerator).

Alternatively, return of cold-chain products could be considered where there is a unique monitoring system attached to the product, which would demonstrate whether the product has been stored outside refrigerated conditions.

If the wholesaler chooses to accept returned refrigerated products then stringent controls must be in place. The IMB will review the policy and practices of the wholesaler during inspection. Further guidance on cold-chain returns is set out in the IMB document entitled ‘[Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances](#)’ available at [www.imb.ie](http://www.imb.ie).

There should be an inventory 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. It is emphasised that, in line with the requirements of EU GDP guidelines, the RP must formally approve the release of returned medicinal products to saleable stock.

Wholesalers should also be aware of the potential for counterfeit medicinal products entering the supply chain through the returns process. All relevant staff members should be made aware of this.

#### 5.6.1 Product disposal

All products that are rejected in house, rejected when received as returns or are recalled should, if instructed accordingly by the MA holder, 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 despatching the product.

There should be an inventory of products placed into waste. Records and certificates of destruction should be maintained.

The use of third party contractors should be managed by a service level agreement.

For disposal of controlled drugs further requirements apply and guidance on this issue may be obtained by contacting the Controlled Drugs unit at the IMB.

#### 5.6.2 Recall

The wholesaler is obliged, in accordance with the Regulations and with GDP guidelines, to have a recall procedure in place. This procedure must be submitted to the IMB when making an application for a wholesaler's authorisation. This is to enable the swift and effective recall from the marketplace of defective and/or potentially harmful medicinal products. The IMB should also be included on the circulation list for the procedure and whenever the procedure is updated the IMB should receive a copy.

The responsibility of the wholesaler will depend on whether they are a primary or secondary distributor of the product.

The procedure should include, at a minimum, the following:

- The role of the RP in the recall,
- Nominated responsibilities for coordination of the recall action,
- 24hr contact numbers for the company (at least three personnel) and the IMB,
- Requirement to discuss with the MA holder, primary wholesaler and the IMB 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;
- Requirement to record batch numbers for wholesale to wholesale transactions;
- 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 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 inventory in place for recalls and also templates of forms and letters for the execution of a recall.

The recall procedure should regularly be challenged to ensure that the process is effective and capable of tracing all customers and products in the event of a recall. This challenge may involve identifying a particular batch of a product and reconciling quantities received of this batch with those in stock and distributed to customers. A mock recall 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.

(For guidance refer to the IMB document entitled ‘[Recall of Medicinal Products for Human and Veterinary Use](#)’ available at [www.imb.ie](http://www.imb.ie)).

## **5.7 Self-Inspection**

It is necessary to conduct and record self-inspections (internal audits) to monitor the implementation of, and compliance with, GDP guidelines. All areas of GDP should be covered within the self-inspection programme.

The manner and frequency of self-inspections should be defined in the self-inspection procedure. At least one self-inspection should be performed annually. A plan/schedule should be documented. Progress against this plan should be monitored and a log of inspections performed should be maintained.

A report on such inspections should be available, which includes a list of follow up actions. Any non-conformance identified should be addressed in writing and closed out in a timely manner.

### **5.8 Customer complaints**

A procedure should be in place describing the process to be followed upon receipt of a complaint. A log of complaints and investigations into these should be recorded. All complaints should be dealt with in a timely manner and the complainant should be informed of the outcome of any investigation.

Customer complaints relating to product quality should be referred to the primary wholesaler and/or the marketing authorisation holder, as appropriate.

Any complaints of a service or distribution nature may be dealt with by the wholesaler. Such complaints may also require input from the primary wholesaler and/or marketing authorisation holder, as appropriate. The Responsible Person should be involved in the investigation of all customer complaints.

### **5.9 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 cannot sell either category of medicinal products 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 should be in compliance with the Medicinal Products (Prescription and Control of Supply) Regulations 2003, as amended. A system to track sales should be in place. A listing of general sale medicinal products is available at [IMB General Sales List](#).

Queries regarding the 'sales-classification' of a medicinal product may also be referred to [compliance@imb.ie](mailto:compliance@imb.ie).

### **5.10 Counterfeit medicinal products**

It is imperative that all wholesalers operate using good governance and display vigilance in their efforts to prevent counterfeit medicinal products 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 suspect counterfeit product or being notified that a (suspect) counterfeit product has been received.
- Be aware of the possibility of counterfeit medicinal products being supplied inadvertently through legitimate sources i.e. other authorised wholesalers.
- Have robust systems for ensuring the legitimacy of their suppliers and ensure that this is 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 for all products.
- Train staff to be aware of counterfeits and what to look out for.
- Ensure that the goods-in procedure involves detailed review of products and 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 wholesaler's authorisation to be used by third parties to source or supply product.
- Be vigilant and not allow themselves to be used by counterfeiters to 'launder' counterfeit 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 counterfeit product through legitimate chains.
- Be aware of the possibility of counterfeit product entering the supply chain through returns.
- Be knowledgeable of products at risk of counterfeiting. should also be made aware of these products.

A wholesaler in possession of a product that is found to be (or suspected of being) counterfeit is responsible for the removal and quarantine of the product from saleable stock. If suspicious that a product is not genuine then the IMB and the marketing authorisation holder should be consulted immediately. It should never be returned to the supplier without the consent of the IMB.

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

### **5.11 Deviations, Corrective and Preventive Actions (CAPA)**

Deviations are non-conformances with GDP, Regulations or in-house procedures. A procedure should be in place detailing the process for documenting, investigating and closing deviations. The RP should be notified of any deviations and an assessment performed to see if there is any effect on the quality of the product or on the quality system.

Corrective and preventive actions (CAPAs) may arise as a result of deviations, self-inspections, observations or from other issues.

A log of deviations should be maintained and all resulting CAPAs documented. CAPAs should be subjected to regular review to ensure their full implementation.

### **5.12 Promotional samples/Sales representatives**

A procedure should be in place describing the controls and traceability system in place for promotional samples and samples maintained by sales representative.

It should be ensured that batch details of medicinal products supplied to sales representatives are recorded and are included in any recall action that may arise. All samples received by sales representatives should be stored as described in section 4.

### **5.13 Physicians' samples**

The Medicinal Products (Control of Advertising) Regulations 2007 (S.I. No. 541 of 2007) permit supply of free samples of medicinal products under defined circumstances to persons qualified to prescribe such products.

Where such samples are stored by an authorised wholesaler, it is expected that the wholesaler will, in conjunction with the marketing authorisation holder, ensure that adequate records are maintained to permit the rapid recall of any batch in the event of that being necessary.

Restrictions on the quantities and product categories/types of such samples that 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.

## **6. 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 IMB in accordance with the Medicinal Products (Control of Placing on the Market) Regulations 2007, as amended. Certain other products are authorised centrally by the European Commission for marketing in all Member States and are the subject of European marketing authorisations granted under EU Regulation 726/2004, as amended.

There are some exemptions in the Medicinal Products (Control of Placing on the Market) Regulations 2007, as amended, 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, as amended and also Paragraph 11 of the Medicinal Products (Control of Placing on the Market) Regulations 2007, as amended. Wholesalers should be aware of these requirements and should have the necessary documentation and systems in place.

(For detailed guidance, refer to the IMB document entitled ‘[Guidance Note for the Notification System for Exempt Medicinal Products](#)’ available at [www.imb.ie](http://www.imb.ie))

## **7. CONTROL AUTHORITY BATCH RELEASE CERTIFICATE**

Under Article 114 of Directive 2001/83/EC, as amended, 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 a Control Authority Batch Release (CABR) certificate for the batch.

This CABR 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 CABR requirements from another Member State of the EEA should receive, along with the documentation for the batch, a copy of the CABR certificate for the batch.

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

An IMB inspector may, in the course of an inspection, ask to see the CABR 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 a CABR certificate does not apply where:

- The wholesaler has been supplied with any relevant batch 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 CABR certificate being received. A list of products requiring a CABR should be maintained and available to all relevant staff (particularly goods-in staff). The member(s) of staff who can permit a batch to be sold should be limited and defined. Those staff members should have the relevant training and expertise.

## **8. HOW TO APPLY FOR THE ISSUE OF OR VARIATION TO A WHOLESALER'S AUTHORISATION**

In order to apply for a wholesaler's authorisation or for a variation to an existing wholesaler's authorisation, the appropriate standard application form should be completed and forwarded to the Compliance Department, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, together with the appropriate fee and any relevant supporting information.

These standard application forms are available from the publications page on the IMB website ([www.imb.ie](http://www.imb.ie)).

Schedule 1 of the Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended, along with the application form for a wholesaler's authorisation, detail the information that must be provided to the IMB for new applications.

For variations submitted to change the name of the RP or to add a deputy RP, a curriculum vitae, role profile and training records (GDP and SOP training) should be submitted to support the application.

For variations to add product categories to an authorisation such as exempt or parallel imported medicinal products, the IMB may request the applicable SOPs for review. An inspection may also be required.

## **9. IMB INSPECTIONS IN RELATION TO APPLICATIONS FOR A NEW WHOLESALER'S AUTHORISATION OR VARIATION**

The completed application is assessed by the IMB. For a new application for authorisation, this assessment consists of an inspection of the premises and the wholesaler's quality system. Assessment of an application for a variation to an existing authorisation may not necessitate an inspection.

The application is reviewed and examined for completeness and the applicant may be contacted to confirm the readiness of the site for inspection if required. A 90 day period is permitted for consideration of the application. Any inspection will be scheduled based upon meeting the 90 day target.

The purpose of an inspection is to confirm that the applicant can meet the conditions of their new/revised wholesaler's authorisation and complies with the provisions of the Regulations relating to the wholesale distribution of medicinal products. New applicants must demonstrate that they comply with GDP.

Within 15 days of the inspection a Deficiency Summary Report (DSR) is sent to the applicant (or authorisation holder) formally notifying any deficiencies found and requesting proposals for corrective actions and timelines for completion. The full inspection report is issued within 28 days of the inspection. The DSR and/or inspection report will detail the timeline within which the applicant is requested to respond to the IMB with details of the corrective actions to be put in place to address the deficiencies observed.

## **10. GRANTING OF AUTHORISATION/VARIATION**

Once an application for a new wholesaler's authorisation has been assessed, the inspection performed, and post-inspection follow up completed, the Management Committee of the IMB considers a recommendation regarding the application. This may be positive or negative depending on the outcome of the inspection and the acceptability of the applicant's responses to any deficiencies identified.

Where approved, the authorisation is issued to the applicant with standard conditions attached.

An application to vary an authorisation may be accepted or rejected depending on the outcome of the IMB's review and of an associated inspection (if required).

## **11. REFUSAL OF AN APPLICATION OR SUSPENSION/REVOCAION OF EXISTING AUTHORISATION**

The Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended, state that the IMB may refuse an application or suspend or revoke an existing wholesaler's authorisation. The procedures for the IMB carrying out any of these actions are described in Schedule 3 to these Regulations.

## **12. FEES PAYABLE**

Fees are payable under the Irish Medicines Board Acts 1995 and 2006.

For new applications an inspection fee will be additional to the application fee. For smaller operations an hourly inspection fee may apply as opposed to the daily rate.

A schedule of the current fees is available from the IMB website (see [fee information](#) in the publications section at [www.imb.ie](http://www.imb.ie)).

## **13. ROUTINE AND NON-ROUTINE INSPECTIONS**

The IMB will inspect an authorised wholesaler's premises on a regular basis. Routine inspections are carried out once every three years. A greater frequency may be applied to large wholesalers or to any wholesaler which exhibits a poor record of GDP compliance.

Non-routine inspections may be carried out as a result of a variation application; a for-cause inspection may be carried out due to non-compliances with the conditions of an authorisation. New wholesalers may also be subject to an inspection approximately 12 to 18 months following the granting of their authorisation.

## **14. CONDITIONS ATTACHING TO A WHOLESALER'S AUTHORISATION**

A wholesaler's authorisation is subject to conditions as specified by the IMB, and may, in particular, require that the authorisation holder complies with those conditions set out in Schedule 2 of the Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended. The conditions attached to a wholesaler's authorisation, at the time of the publication of this guide, are very closely based on those set out in Schedule 2.

## **15. USEFUL INFORMATION**

The IMB's website ([www.imb.ie](http://www.imb.ie)) contains a listing of all wholesalers and their current status (authorised, suspended, withdrawn or revoked). Details listed include the name and address of the authorisation holder, the address of the site of wholesaling, the date on which the authorisation was last granted and the categories of medicinal products covered by the authorisation.

Also included on the IMB's website is a list of medicinal products currently authorised in Ireland. A list of products classified as general sale can be obtained here along with other products holding a Product Authorisation (PA), Parallel Product Authorisation (PPA) or Dual Pack Import Registration (DPR). The authorisation holder for each product is also stated.

### **15.1 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. All risk assessments should be carried out by competent personnel and should be reviewed and approved by relevant personnel, including the RP.

Companies using risk management should have a procedure in place and training should be performed on its use. 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 the ICH Harmonised Tripartite Guideline entitled 'Quality Risk Management – Q9' should be consulted. This document is available for download at [www.ich.org](http://www.ich.org).

## 15.2 Controlled drugs

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), annual licences,
- Cycle count checks,
- 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 licence/registration,
- Theft/shortage,
- Certification of the controlled drug safe by An Garda Síochána.

## 15.3 New EU legislative proposals

Directive 2011/62/EU of the European Parliament and of the Council amending Directive 2001/83/EU of the Community Code relating to medicinal products for human use as regards the prevention of the entry into the legal supply chain of falsified medicinal products, was published on 1 July 2011. It is due for gradual implementation from July 2012 onwards. The directive can be downloaded from the following link,

[http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_2011\\_62/dir\\_2011\\_62\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf)

This amending legislation provides for additional measures to protect the legal supply chain from being infiltrated by substandard and counterfeit medicines. This may impact on the GDP operations of wholesalers and this guide will be updated as the legislation is implemented.

Updating of the EU GDP guidelines is also in progress in order to correspond with this new legislation.

## APPENDIX 1

Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended

A summary of Regulations 1 to 15 as set out in these regulations is outlined below:

- Regulation 1 The name of the Regulations – the Medicinal Products (Control of Wholesale Distribution) Regulations 2007, as amended.
- Regulation 2 Date of coming into force of the Regulations.
- Regulation 3 Revocation of previous Regulations.
- Regulation 4 Definitions.
- Regulation 5 The statement that no person will keep or offer for sale by wholesale, or sell by wholesale, any medicinal product except in accordance with a wholesaler's authorisation.
- Regulation 6 Exemptions from requirement for a wholesaler's authorisation (see section 4 of this guide).
- Regulation 7 Procedure for application for a wholesaler's authorisation.  
A wholesaler's authorisation may be granted following receipt of an application by the IMB and demonstration by the applicant that they have suitable premises, equipment and staff. Also suitable arrangements for record-keeping, handling, storage and distribution.  
Note: this is achieved by the applicant demonstrating compliance with the guidelines on Good Distribution Practice. (Refer to Appendix 2).  
The Regulation also sets out requirement for fees to be paid to the IMB in respect of the application. (Refer to section 13 of this guide on Fees Payable).
- Regulation 8 Procedure for the IMB's consideration of an application for a wholesaler's authorisation.  
Defines the period of time that the IMB has for consideration of a new wholesaler's authorisation as 90 days. This also includes provision for the IMB to inspect the wholesale operation to ensure that the information in the application is correct and to request further information, if required.

- Regulation 9** Procedure for the IMB's granting or refusal of a wholesaler's authorisation.  
Defines the IMB's powers for granting an authorisation. This Regulation also defines the IMB's powers to grant an authorisation other than in accordance with the application and to refuse an application. The procedures and timing for refusing an authorisation or granting an authorisation other than in accordance with the application are also defined.
- Regulation 10** The application and effect of a wholesaler's authorisation.  
Defines the scope of a wholesaler's authorisation, i.e. may relate to all medicinal products or to specific classes of medicinal products. Where applicable, the authorisation will also state the name of the product authorisation (PA) holder where the wholesaler is the agent for that PA holder or where the wholesaler is responsible for first making a product available to the Irish market, i.e. where the product is not received from an Irish based wholesaler or manufacturer.
- Regulation 11** The obligations to be met by the holder of the wholesaler's authorisation.  
This includes provision for the general conditions which are attached to a wholesaler's authorisation, as specified in Schedule 2 to the Regulations. These conditions are reproduced in Appendix 1 to this guide. Other specific conditions may also be attached to the authorisation by the IMB, as appropriate.
- Regulation 12** Procedure for variation of a wholesaler's authorisation.  
This sets out the procedure to be followed by an authorisation holder in varying the authorisation to change the range of medicinal products handled by the operation, the nature of the wholesale operation, premises etc.  
The IMB has up to 90 days for consideration of a variation application and may inspect the wholesale operation to ensure that the information in the application is correct and may also request further information, if required.  
Regulation 12 also set out powers that the IMB has to vary the authorisation other than in accordance with the application, or to impose a variation on an authorisation. The procedures and timing for these processes are also defined.

**Regulation 13** Procedure for suspension or revocation of a wholesaler's authorisation.

Regulation 13 sets out the powers available to the IMB to suspend or revoke an existing wholesaler's authorisation. The grounds on which suspension and or revocation may be warranted are described and include:

- The authorisation holder is not carrying out the wholesale operation or has given the IMB notice to this effect.
- The information supplied in the application for the authorisation was false or incomplete.
- Failure to comply with the conditions of the authorisation.
- The suspension may be imposed in full or may be limited to the particular aspects of the wholesale distribution operation. The Regulation also defines the procedure and timing for the suspension and revocation processes.

**Regulation 14** Outlines particular enforcement obligations on the IMB to investigate that:

- (a) All wholesalers of medicinal products have obtained a wholesaler's authorisation
- (b) That wholesalers are complying with the terms and conditions of the authorisation
- (c) That the wholesaler is complying with the obligations under Regulation 11

**Regulation 15** Sets out transitional provisions for authorisations granted prior to the 2007 Regulations coming into force.

#### Enforcement of these Regulations

The IMB is responsible for the inspection and authorisation of wholesaling activities under these Regulations. Powers of entry and enforcement are set out in Article 32b of the Irish Medicines Board Act 1995 and 2006. While the IMB has the primary role in enforcing these Regulations, the following also have powers in this regard:

- officers of the Minister for Health,
- Health Boards and their officers and,
- in defined circumstances, the Pharmaceutical Society of Ireland and its officers.

## APPENDIX 2

### Directives, Acts, Regulations Pertaining to the Wholesaling of Medicinal Products

1. Irish Medicines Board Act, 1995 (No. 29 of 1995)
2. Irish Medicines Board Act, 1995 (Commencement) Order, 1996 (S.I. No. 40 of 1996)
3. Irish Medicines Board (Competent Authority) Order, 1998 (S.I. No. 143 of 1998)
4. Irish Medicines Board (Miscellaneous Provisions) Act, 2006 (No. 3 of 2006)
5. Medicinal Products (Control of Wholesale Distribution) Regulations, 2007
6. Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2009
7. Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2010
8. Medicinal Products (Control of Placing on the Market) Regulations, 2007
9. Medicinal Products (Control of Placing on the Market) Regulations, 2007 (Amendment) Regulations 2009
10. Medicinal Products (Control of Placing on the Market) Regulations, 2007 (Amendment) Regulations 2010
11. Medicinal Products (Control of Advertising) Regulations, 2007
12. Medicinal Products (Control of Manufacture) Regulations, 2007
13. Medicinal Products (Control of Manufacture) Regulations, 2007 (Amendment) Regulations 2009
14. Medicinal Products (Control of Manufacture) Regulations, 2007 (Amendment) Regulations 2010
15. Medicinal Products (Prescription and Control of Supply) Regulations, 2003 (S.I. No. 540 of 2003), as amended
16. European Parliament and Council Directive 2001/83/EC of the community code relating to medicinal products for human use.
17. EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C63/03)
18. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended
19. Misuse of Drugs Regulations, 1988 (S.I. No. 328 of 1988)

### APPENDIX 3

#### List of Abbreviations

ACHM	-	Advisory Committee for Human Medicines
CABR	-	Control Authority Batch Release
DPR	-	Dual Pack Import Registration
EEA	-	European Economic Area
EMA	-	European Medicines Agency
EU	-	European Union
GDP	-	Good Distribution Practice
GMP	-	Good Manufacturing Practice
ICH	-	International Conference on Harmonisation
INCB	-	International Narcotics Control Board
IMB	-	Irish Medicines Board
MA	-	Marketing Authorisation
MAH	-	Marketing Authorisation Holder
PA	-	Product Authorisation
PPA	-	Parallel Product Authorisation
SOP	-	Standard Operating Procedure
RP	-	Responsible Person
WA	-	Wholesaler's Authorisation