HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Wholesaling and Brokering of Medicinal Products for Human Use in Ireland

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CONTENTS

1 SCOPE

The purpose of this document is to provide guidance on the regulations covering the wholesale distribution and brokering 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, Food and the Marine 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, (S.I. No. 538 of 2007)*, and Directive 2001/83/EC*). Wholesale and distribution of medicinal products are considered to be synonymous.

The table below further defines the activities that constitute wholesaling. Definitions are taken from the Annex of the European Commission Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (2013/C 343/01).

Terms	Definition
Procuring	Obtaining, acquiring, purchasing or buying medicinal products from manufacturers, importers or other wholesale distributors
Holding	Storing medicinal product
Supplying	All activities of providing, selling, donating medicinal product to wholesalers, pharmacists, or persons authorised or entitled to supply medicinal products to the public
Export procedure	Allow Community goods to leave the customs territory of the Union. For the purposes of these guidelines, the supply of medicines from an EU Member State to a contracting State of the European Economic Area is not considered as export.

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 should comply with the Regulations, Directives and guidelines discussed in this document.

**as amended*

It should be noted that no exemptions exist for marketing authorisation holders or regulatory offices, unless they are located at the site of manufacture of the product being wholesaled.

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.

Brokering of medicinal products for human use 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. A company conducting any such activities in relation to human medicines is considered a broker and must comply with the requirements for brokers set out in the Medicinal Products (Control of Wholesale Distribution) Regulations 2007, (S.I. No. 538 of 2007)* and Directive 2001/83/EC*.

3 WHOLESALE DISTRIBUTION

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 and other wholesalers.

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 the 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.

It is important to note that the definition of wholesaling includes reference to procurement and supply, both of which may not necessarily involve the physical handling of medicines and may only relate to the financial transactions carried out at an office. This can involve, for example, purchasing the medicinal product from the manufacturer and selling it on to the primary wholesaler or outsourcing the storage of medicinal product on a consignment basis to a wholesaler. Such activities require a WDA and it should be noted that there are no exemptions for marketing authorisation holders or regulatory offices.

4 BROKERING

Brokers, as defined in section 2 above, should not to be confused with wholesalers that do not physically handle the products but procure and supply them via financial transactions. As mentioned above, such financial activities constitute wholesaling and require a WDA in Ireland. Brokers never procure (purchase) and/or supply (sell or physically supply) medicines but are involved in facilitating such transactions between two parties independent of the broker.

Brokers of medicinal products located in Ireland must be registered as a broker with the HPRA and should comply with the relevant Regulations, Directives and guidelines. The HPRA has published guidance on the GDP requirements to be met by brokers 'Guide to Good Distribution Practice of Medicinal Products for Human Use', available on the ~~'~~Publications and ~~Forms'~~Forms section at www.hpra.ie.

Further clarification on what constitutes brokering is available in the Publications and Forms section of the HPRA website.

5 LEGISLATIVE BASIS

At European level the legislative basis for both the 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 2007, (S.I. No. 538 of 2007)* transpose the requirements of Title VII of Directive 2001/83 EC* 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, 2010, 2012, 2013 and 2019 as outlined in the table below.

Amending ~~S.I.~~	Details of amendment
Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2009 (S.I. No. 2 of 2009)	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.
Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2010 (S.I. No. 286 of 2010)	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.
Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2012 (S.I. No. 274 of 2012)	The 2012 amendment clarified the method for the HPRA conducting inspections.
Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2013 (S.I. No. 164 of 2013)	The 2013 amendment gives effect to Directive 2011/62/EU which amends Directive 2001/83/EU. This amending legislation provides for additional measures to protect the legal supply chain from being infiltrated by substandard and falsified medicines and introduces requirements for brokers.
Medicinal Products (Safety Features on Packaging) Regulations 2019 (S.I. No. 36 of 2019)	The first 2019 amendment gives effect to Commission Delegated Regulation (EU) 2016/161 and designates the Health Products Regulatory Authority (and in some cases also the Pharmaceutical Society of Ireland) as the competent authority responsible for enforcing Commission Delegated Regulation (EU) 2016/161 of 2 October 2015. In addition, it provides for the verification and decommissioning of the unique identifier of a medicinal product by a wholesaler before supply in certain circumstances.
Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (Amendment) Regulations 2019 (S.I No. 217 of 2019)	The second 2019 amendment updates the obligations on holders of wholesaler's authorisations to allow for greater traceability and transparency in the wholesale distribution supply chain and it makes the necessary amendments associated with enabling the importation of exempt medicinal products from third countries by holders of wholesaler's authorisations.

Together, these Regulations may be cited as the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (S.I. No. 538 of 2007)*. For the purposes of this guideline these collectively will be hereinafter referred to as the 'Regulations'.

The Health Products Regulatory Authority (HPRA) 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, 52 St. Stephen's Green, Dublin 2; or may be viewed and downloaded from the Attorney General's website.

6 WHEN IS A WHOLESALE DISTRIBUTION AUTHORISATION NOT REQUIRED?

(i) A registered pharmacy that sells or supplies a medicinal product in accordance with a registered doctor's or registered dentist's prescription does not require a WDA.

(ii) Retailers selling authorised medicinal products directly to the public do not require a WDA. 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 WDA. 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 WDA requirements. The exemption applies where the company's legal entity, which includes the warehousing operation, is registered as a retailer.

(iii) The holder of a manufacturer's authorisation ~~issued by the HPRA~~ does not require a WDA if it only distributes products manufactured at the manufacturing site and all wholesaling activities are performed at the manufacturing site under the manufacturer's authorisation.

However, a manufacturer must hold a WDA 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 WDA if involved in distribution of a medicinal product manufactured in its entirety by another manufacturer.

(iv) A WDA 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 registered medical practitioner
- a registered dentist
- a registered dispensing optician
- a registered optometrist
- a registered veterinary surgeon
- a person who is acting as a pre-hospital emergency care provider
- a person lawfully entitled to obtain medicinal products for administration to patients in the course of a business as a hospital

(v) A WDA issued by the HPRA is not required for holders of a WDA issued by the competent authority of another EEA Member State which distribute directly to their customers in Ireland from that other State.

(vi) A WDA 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)*.

(vii) A logistics service provider involved in the transport 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 outside of the EEA or to an authorised wholesaler for products imported from within the EEA. However, if a logistics service provider 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 logistic service provider may be regarded as falling within wholesale authorisation requirements.

For clarification as to whether a particular activity is subject to wholesale regulatory requirements, advice may be sought from the HPRA at compliance@hpra.ie.

7 HOW TO APPLY TO REGISTER AS A BROKER OF MEDICINAL PRODUCTS

Brokers operating within the Irish state are required to register with the HPRA. In order for a broker to be included on the HPRA brokers register they must submit an application form. Details regarding the application assessment process are detailed in a guidance note 'Guide to Registration Requirements for Brokers of Medicinal Products in Ireland'. Both the application form and the guidance can be found on the ~~'~~Publications and ~~Forms'~~Forms section at www.hpra.ie.

8 HOW TO APPLY FOR THE ISSUE OF, OR VARIATION TO, A WHOLESALE DISTRIBUTION AUTHORISATION

In order to apply for a WDA or for a variation to an existing WDA, complete the appropriate application form and forward to the Compliance Department, together with the appropriate fee and any relevant supporting information. These application forms are available on the HPRA website (www.hpra.ie).

Schedule 1 of the Medicinal Products (Control of Wholesale Distribution) Regulations 2007*, along with the application form for a WDA, details the information that must be provided to the HPRA for new applications. The HPRA can only grant a WDA where wholesaling operations are carried out in Ireland.

For variations submitted to change the name of the RP or to add a deputy RP, a curriculum vitae, signed 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 HPRA may request the applicable SOPs for review. An inspection may also be required.

The HPRA has published guidance on the requirements 'Guide to New Applications and Variations to Wholesale Distribution Authorisations' and 'Guide to Good Distribution Practice of Medicinal Products for Human Use' which are available on the ~~'~~Publications and ~~Forms'~~Forms section of the HPRA website (www.hpra.ie).

9 HPRA INSPECTIONS IN RELATION TO APPLICATIONS FOR A NEW WHOLESALE DISTRIBUTION AUTHORISATION OR VARIATION

The completed application is assessed by the HPRA. 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 require 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 WDA and complies with the provisions of the Regulations relating to the wholesale distribution of medicinal products. New applicants must demonstrate that they comply with

Good Distribution Practice (GDP). See 'Guide to Good Distribution Practice of Medicinal Products for Human Use' for further information regarding GDP requirements, available on the ~~'~~Publications and ~~Forms'~~Forms section at www.hpra.ie.

Within 15 days of the inspection an inspection report is sent to the applicant (or WDA holder) formally notifying any deficiencies found and requesting proposals for corrective and preventative actions and timelines for completion. The inspection report will detail the timeline within which the applicant is requested to respond to the HPRA with details of the corrective and preventative actions to be put in place to address the deficiencies observed.

10 GRANTING OF AUTHORISATION/VARIATION

Once an application for a new WDA has been assessed, the inspection performed, and post-inspection follow-up completed, the Management Committee of the HPRA 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. The WDA will also be published to the EudraGMDP database.

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

11 REFUSAL OF AN APPLICATION OR SUSPENSION/REVOCATION OF EXISTING AUTHORISATION

The Medicinal Products (Control of Wholesale Distribution) Regulations 2007, (S.I. No. 538 of 2007)* state that the HPRA may refuse an application, or suspend or revoke an existing WDA. The procedures for the HPRA 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 on the ~~'~~Publications and ~~Forms'~~Forms section at www.hpra.ie.

13 ROUTINE AND NON-ROUTINE INSPECTIONS

The HPRA will inspect an authorised wholesaler's premises on a regular basis. Routine inspections are carried out at least 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 GDP CERTIFICATES

Inspections related to new applications for a WDA and routine GDP inspections at existing WDA holder premises, will be issued with a GDP certificate or a 'statement of non-compliance with GDP' as appropriate. The documents are ~~also~~ published to the EudraGMDP database.

Non-routine inspections do not result in the issuance of a GDP certificate, but may result in the issuance of a 'statement of non-compliance with GDP'.

15 CONDITIONS ATTACHED TO A WHOLESALE DISTRIBUTION AUTHORISATION

A WDA is subject to conditions as specified by the HPRA, 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*. The conditions attached to a WDA at the time of the publication of this guide, are very closely based on those set out in Schedule 2.

16 USEFUL INFORMATION

The HPRA's website (www.hpra.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 HPRA'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.

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