

Guide to The Notification System for Exempt Medicinal Products



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1 SCOPE

This document gives guidance in the area of exempt (unauthorised) medicinal products and their sourcing and supply to the Irish market. It describes the system for notification to the Health Products Regulatory Authority (HPRA) of the receipt or importation of exempt medicinal products that are intended to be supplied in Ireland for human use.

This guidance applies principally to wholesalers and manufacturers that receive or import exempt medicinal products. It may also be of interest to healthcare professionals wishing to understand the requirements around obtaining such exempt medicines.

2 INTRODUCTION

Subject to certain exemptions, medicinal products that are placed on the Irish market are required to have a marketing authorisation issued by the HPRA (reflected by a PA number) or, in the case of centrally authorised (pan-European) products, an authorisation issued by the European Commission, reflected by an EU number (ref: regulation 6 of the Medicinal Products (Control of Placing on the Market) Regulations 2007). Schedule 1 to these regulations includes an exemption for practitioners to prescribe unauthorised medicinal products for individual patients under their direct responsibility, in order to fulfil the special needs of those patients. Such products are defined as 'exempt medicinal products'.

The relevant Regulations are:

- Medicinal Products (Control of Wholesale Distribution) Regulations 2007, S.I. No. 538 of 2007
- Medicinal Products (Control of Manufacture) Regulations 2007, S.I. No. 539 of 2007
- Medicinal Products (Control of Placing on the Market) Regulations 2007, S.I. No. 540 of 2007

An 'exempt medicinal product' is defined as 'a medicinal product to which paragraph 2 of Schedule 1 of the Medicinal Products (Control of Placing on the Market) Regulations 2007, or any equivalent legislation in any EEA State other than the State, applies'. The aforementioned Paragraph 2 of Schedule 1 states that an exempt medicinal product may be sold or supplied '...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...'

This means that a medicinal product can only be defined as 'exempt' when it is supplied to the order of a registered doctor or registered dentist for use by their individual patients under their direct personal responsibility. Currently nurse prescribers are not permitted to prescribe exempt medicinal products.

The notification system permits the HPRA to maintain a database of exempt products. This is particularly important where we receive a notification of a quality defect (or other type of non-compliance issue) in a medicine from another market. Having the database permits us to check if the product concerned has been imported and supplied to Irish patients and, where it has, we can institute appropriate risk-mitigating measures (such as a product recall) in order to protect those patients.

3 GENERAL REQUIREMENTS

Holders of wholesale distribution authorisations are permitted to source exempt medicinal products from within the European Economic Area (EEA). Only holders of manufacturing authorisations are permitted to import exempt medicinal products from non-EEA countries. Note that both types of authorisation must have this type of activity specified within the scope of the authorisation.

Wholesalers and manufacturers that receive an order to supply an exempt medicinal product within Ireland should obtain confirmation (written or otherwise) that the supply is 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'. It is not a requirement to request details of patient names or patient ID numbers. The practitioner is not required to sign the confirmation. The exact nature of the confirmation is at the discretion of the wholesaler or manufacturer intending to supply the exempt medicinal product within Ireland, but must be available for review by HPRA inspectors during an inspection.

An exempt product may not be prescribed or supplied in situations where an authorised equivalent (i.e. same active substance(s), strength and dosage form) is available in Ireland. This is in accordance with the judgement in European Court of Justice case_C-185/10_Commission v Poland.

In circumstances where a practitioner prescribes an authorised product which has previously been in short supply and had been temporarily replaced by an exempt product, it is important that the pharmacist, and in turn the wholesaler, establish the current availability of the authorised product. Section 3.2.3 of the [Pharmaceutical Society of Ireland guidelines on Sourcing, Storage and Disposal of Medicines, 2011](#) addresses this issue for pharmacists.

It is essential that all healthcare professionals in the supply chain are aware that exempt medicinal products have not been assessed by the HPRA against the criteria of safety, quality and efficacy, and that the responsibility for the clinical use of such products lies with the prescriber. Particular attention should be paid to different expressions of strengths and the potential presence of allergens in exempt products that may not have the list of ingredients present in the English language.

4 NOTIFICATION SYSTEM FOR EXEMPT MEDICINAL PRODUCTS

The Medicinal Products (Control of Wholesale Distribution) Regulations 2007 and the Medicinal Products (Control of Manufacture) Regulations 2007 require wholesalers and manufacturers that receive or import, respectively, exempt medicinal products to notify the HPRA of their receipt. Notification is currently required within two working days of receipt of the consignment and must be communicated to the HPRA electronically via its exempt products database. Guidance on how to register with the system and how to upload notifications is detailed in Appendix I of this guide.

Charges apply to users of the exempt products database. A fee is charged on each occasion that a product is notified to the HPRA. These fees are charged annually based on the number of product notifications made in a calendar year. There is no fee for initial registration. For more information please see the 'Guide to Fees' for the current year at www.hpra.ie.

Wholesalers that receive exempt medicinal products from other EEA Member States and distribute those products to the Irish market via other wholesalers are required to notify the sourcing of those products to the HPRA.

The requirement to notify the HPRA applies only to receipt of 'exempt' medicinal products intended for distribution in Ireland. Therefore, the receipt of unauthorised medicinal products for onward export to other markets (both to EEA and third countries) does not need to be notified to the HPRA.

However, in situations where a wholesaler receives a consignment of unauthorised product, part of which is destined for re-export and part of which is for supply to the Irish market (as 'exempt'), the wholesaler is obliged to notify the HPRA of the receipt of the product to be supplied in Ireland as 'exempt' as described above.

Holders of Irish manufacturers' authorisations that manufacture and supply unauthorised compounded products are not required to notify details of every product supplied. Such manufacturers are required to notify the HPRA with details of any unauthorised medicinal products that they use as ingredients of the compounded product (i.e. each product name, active substance(s) and the name of the manufacturer). Regular updates are required if there are any changes to those starting materials and should be e-mailed in spreadsheet format to ep@hpra.ie.

Appendix II of this guide shows the situations in which exempt medicinal product notifications must be made to the HPRA and clarifies some areas where notification is not required. It also gives detailed instruction on how to register with the notification system and how to make the notifications.

Note: currently, there is no requirement in Irish law for healthcare professionals to notify the HPRA where they have directly imported an unauthorised medicine from a wholesaler or

manufacturer outside of Ireland (but within the EEA) for the treatment of a patient. In circumstances where a recall of an exempt medicinal product is required, and units of that exempt product have been imported directly by a healthcare professional without notification to the HPRA, the HPRA will generally have no knowledge that those affected units are on the Irish market, and this may lead to those units not being covered by the recall. We accept and encourage voluntary notifications from healthcare professionals.

5 PRODUCTS IN PHASE III CLINICAL TRIALS

Investigational medicinal products used in Phase III clinical trials may be supplied as exempt medicines. However, these should be appropriately packaged and labelled* to ensure that there is sufficient information for the prescriber, pharmacist and the patient to ensure their safe use. This should include at least the international non-proprietary name (INN) of the active substance as well as the product name, strength and pharmaceutical form. In addition, any reference on the labelling to a clinical trial should generally be removed.

*Note: the labelling of clinical trial products sometimes does not provide the active ingredient name (or its INN), or the product name, and sometimes only include an alphanumeric product reference number on the packaging.

6 ADVERTISING OF EXEMPT MEDICINAL PRODUCTS

The advertising of the sale or supply of exempt medicinal products is not permitted. This is referred to in the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007). This states that 'no advertisement or representation relating to the medicinal product is issued with a view to it being seen by the general public in the State and that no advertisement relating to the products, other than one that states only the trade name, pack size, price and dose, is issued at the request or with the consent of the person selling the product by retail or by way of wholesale dealing or the person who manufactures it and that the sale or supply is in response to a bona fide unsolicited order'.

7 TSE REQUIREMENTS

Although there is no national legislation governing the transmissible spongiform encephalopathies (TSE) certification of exempt products, the HPRA expectation is that authorisation holders sourcing products from a third country must be able to provide assurance before supply that the starting materials comply with the European Commission's TSE guidance. In circumstances where this documentation is not available, the authorisation holder should advise the prescriber (and pharmacist) of this fact in writing prior to supply.

8 PROVISION OF TRANSLATIONS OF PRODUCT INFORMATION

In the circumstance where the exempt medicinal product being supplied has non-English labelling, wholesalers may wish to supply translations of the product information, such as the summary of product characteristics (SPC) and/or package leaflet. These translations should be obtained by the wholesaler from the applicable marketing authorisation holder's Regulatory Affairs department, its Medical department or its Medical Information Office and it should be confirmed that the translation provided is in-line with the approved SPC and/or product information leaflets for the market in question. Where there is no marketing authorisation in any market, regulatory personnel within a manufacturing facility could supply this information.

If it is not possible to obtain such translations via these routes, alternative approaches can be agreed with the HPRA in exceptional cases. From the HPRA's perspective, the risk of using an alternative translation service is that, while the translators may be accredited, there can be doubt as to whether such translators would be aware of the nuances of dosing instructions such as micrograms versus milligrams, or of the significance in a change in medical terminology from a safety perspective.

9 REQUIREMENTS SPECIFIC TO COMPOUNDED MEDICINAL PRODUCTS

Examples of compounded products are patient-specific sterile preparations of cytotoxics, analgesics, antibiotics or parenteral nutrition. Holders of manufacturers' authorisations issued by the HPRA which manufacture and distribute compounded products are not required to notify details of every product supplied. They are required to notify certain details and these are outlined in Appendix II below.

Wholesalers supplying exempt products which are compounded by the holders of Irish manufacturers' authorisations are not required to notify the HPRA of the supply of those products.

In contrast, wholesalers supplying exempt products which are compounded by manufacturers based outside Ireland are required to comply with all aspects of the notification system.

10 PHARMACOVIGILANCE REQUIREMENTS

A wholesaler or manufacturer is required to make and maintain written records relating to details of any suspected adverse reaction to an exempt medicinal product sold or supplied, of which they become aware.

It is the responsibility of the manufacturer which has notified an exempt medicinal product to report such reactions to EudraVigilance. Wholesalers or manufacturers who are not registered

with EudraVigilance may inform the HPRA directly of any adverse reactions. Details of how to report suspected adverse reactions to the HPRA are available on the HPRA website (www.hpra.ie). An online reporting mechanism is also available via our website.

Where a wholesaler, that is not the notifying wholesaler/manufacturer, becomes aware of a suspected adverse reaction relating to an exempt product which it has sourced from the notifying Irish wholesaler/manufacturer, that wholesaler should bring the suspected adverse reaction, without delay, to the attention of the notifying wholesaler or manufacturer. In this way, the notifying wholesaler/manufacturer can fulfil its responsibility and report the adverse reaction. See Appendix II for clarification of when a wholesaler/manufacturer is considered to be the notifying wholesaler/manufacturer.

In order to meet the above obligations, the notifying wholesaler/manufacturer should ensure that appropriate systems and procedures are in place to facilitate receipt, follow-up, recording and prompt notification of suspected adverse reactions in accordance with agreed international formats and terminology for presentation of adverse reaction reports.

All staff should be trained on the procedures in place to receive and record adverse reaction reports, as these may be notified through a variety of sources.

Suspected adverse reactions pertaining to exempt medicinal products compounded under an Irish manufacturer's authorisation should always be reported to EudraVigilance by the manufacturing authorisation holder.

11 REPORTING OF SUSPECTED QUALITY DEFECTS

Wholesalers or manufacturers that source exempt medicinal products are required to inform the HPRA of any suspected quality defect which comes to their attention. Please note that it is the responsibility of the exempt medicinal product notifying wholesaler or manufacturer to inform the HPRA.

Where a wholesaler or manufacturer that is not the notifying company becomes aware of a suspected quality defect pertaining to an exempt product which it has sourced from the notifying wholesaler/ manufacturer, it should bring the quality defect, without delay, to the attention of the notifying wholesaler/manufacturer. Please see Appendix II for clarification of when a wholesaler/manufacturer is considered to be the notifying wholesaler/manufacturer.

The regulations also require wholesalers and manufacturers to maintain written records of the details of any suspected quality defects relating to exempt products sold or supplied by them. This requirement relates to all wholesalers or manufacturers involved in the supply of exempt products, regardless of whether or not they are the notifying wholesaler/manufacturer.

For Irish compounding facilities that are not required to notify compounded products they manufacture, the normal reporting requirements, as outlined in the 'Guide to Reporting Quality Defects' (see the 'Publications and Forms' section on www.hpra.ie) still apply.

Details of how to report suspected quality defects are available on the HPRA website (www.hpra.ie). An online reporting mechanism is also available via our website.

12 CONTACT DETAILS

For further information, contact:

Market Compliance Section
Compliance Department
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Terrace
Dublin 2
Tel: +353-1-6764971
Fax: +353-1-6767836
E-mail: ep@hpra.ie

APPENDIX I NOTIFICATION PROCESS

Step 1: Registration

Each wholesaler or manufacturer must provide company information in order to access the notification system. The information must include the following:

- company name (i.e. the name of the wholesaler or manufacturer intending to submit exempt medicinal product notifications to the HPRA)
- full address of the company
- manufacturing or wholesaler's authorisation number
- contact name, e-mail address and phone number

Once received, an account is set up by the HPRA for that company and an e-mail with a username, password and company notifier code (required to access the notification system) is provided.

Step 2: Notification spreadsheet

The information to be notified (as detailed below) must be entered into a pre-formatted spreadsheet or XML file. The spreadsheet template should be downloaded from the HPRA website. A link to its location is provided during registration. It is not possible for the HPRA to accept the information in any alternative format.

Once the spreadsheet has been completed, the registered user should log on to the HPRA website and upload the completed notification spreadsheet. The spreadsheet file must be named using the following naming convention:

ABCD_ddmmyyyy.xls

where ABCD represents the company registration number for the exempt medicinal product notification scheme, and where 'ddmmyyyy' represents the date of notification e.g. if the company is assigned the registration number 1234 and the date of the exempt medicinal product notification is 1 July 2014 then the file should be named *1234_01072014.xls*.

Once uploaded, an automated e-mail confirming the receipt of the spreadsheet file will be sent to the registered user. This is not an indication of a valid notification. A subsequent e-mail will be sent to the notifying wholesaler or manufacturer, confirming either the validity of the notification, or requesting that the details be resubmitted.

This subsequent e-mail may indicate that some details of that product have changed since the last time it was notified to the system. Robust processes should be in place to ensure that the automated messages received are reviewed and relevant potential errors highlighted by the system are identified and rectified when required.

Duplicate files, or those containing errors or omissions, may be deleted from the database by e-mailing a request to ep@hpra.ie. The reason why deletion is required, as well as the file name and time and date of upload should be included. The amended file should not be re-uploaded until confirmation of deletion is received from the HPRA.

Once amended the file should be re-named to include the word 'amended' in the format '1234_01072014 amended.xls' before re-uploading to the database. Deleted files should be re-uploaded by close of business on the same day as the deletion has been confirmed by the HPRA.

The spreadsheet is separated into five worksheets as follows:

Sheet 1: Product information

Notifying company code (mandatory): this is the code which is provided by the HPRA following company registration.

Notifier product code (mandatory): this is the code which the wholesaler or manufacturer uses to identify the product. There will be an individual product code for each different exempt medicinal product. This notifier product code must be entered on sheets 1 to 5 so that there is a link between all pages of the spreadsheet.

Product name, exactly as labelled (mandatory): this must be the labelled name of the exempt medicinal product. The labelled name may be the brand name, the common name, the scientific name, or any other name, if different, under which the particular medicinal product is labelled. In the case of products such as pre-filled syringes or solutions for injection, the product name must also include the strength per volume of the product.

Strength and unit (mandatory): this is the strength of the product, followed by the unit of measurement for that strength. Examples are as follows:

- '2mg/ml' for an injectable solution
- '100mg/5ml' for an oral suspension containing 100mg per 5ml spoonful
- '250mg per 24 hours' for a transdermal patch
- '1g/ml' for an injectable solution

When entering products which have more than one active constituent, enter the combined strength.

It is not necessary to include strengths when notifying compounded products which are manufactured outside Ireland.

Pharmaceutical form (mandatory): the form of the medicinal product. Examples are as follows:

- tablets
- capsules

- oral suspension
- powder for solution for injection
- suppositories

Pack size (mandatory): Examples are as follows:

- '10 x 5ml' for a pack containing ten 5ml ampoules of an injectable solution
- '1 x 150ml', for a pack containing one 150ml bottle of an oral liquid
- '1 x 28', for a pack containing 28 capsules
- '1 x 1', for a pack containing one implant
- '1 x 2 fl oz', for a pack containing one bottle of a sub-lingual liquid

Number of packs (mandatory): the number of packs sourced. Examples are as follows:

- '6' packs of the above-mentioned injectable solution
- '1' pack of the above-mentioned oral liquid
- '30' packs of the above-mentioned capsules
- '3' packs of the above-mentioned implant
- '1' pack of the above-mentioned sub-lingual liquid, etc.

Trading style (mandatory): enter the trading style (i.e. the company that markets the product). In the case of products authorised in Europe, this will be indicated on the pack as 'Marketing authorisation holder' or 'PL holder'.

Country of authorisation (non-mandatory): this is the country in which the pack is authorised, if any. Please type the full name of the country as per ISO standard (e.g. United Kingdom, France, United States, Netherlands, Germany, etc.). In exceptional cases, it may be that the exempt medicinal product is not authorised in any country, in which case this cell will remain blank.

Sheet 2: Active constituent information

Active constituent (mandatory): each active constituent of the exempt medicinal product must be provided. Where there is more than one active constituent in the exempt medicinal product, each active constituent must be stated, one active per line. Please ensure that the spelling of the active constituent(s) is exactly as stated on the label of the product, even if the label is not in English.

Sheet 3: Batch number and expiry date information

Batch number, exactly as labelled (mandatory): enter the batch number(s) of each product supplied, exactly as it is shown on the packaging of the exempt medicinal product. For exempt medicinal products which have been over labelled or re-packaged by a parallel

importer, the correct system for reporting is to record both batch numbers on two separate lines with the corresponding source in brackets beside the number in the format, as follows:

Line 1: XXXX (Originator)

Line 2: XXXX (Parallel Importer)

Expiry date, exactly as labelled (mandatory): enter the expiry date(s) of the product, exactly as it is shown on the packaging of the exempt medicinal product. For the purposes of this notification system the terms 'Best before' and 'Use before' are considered to be equivalent. For example:

'Expiry date: 11/16' should be entered as '11/2016';

'Use before: Nov 16' should be entered as 'Nov 2016'.

Date of receipt (mandatory): enter the date on which the exempt medicinal product was physically received by the wholesaler or manufacturer (in the format dd/mm/yyyy). In the case of non-Irish wholesalers or manufacturers supplying exempt products to Ireland, enter the date of dispatch to Ireland.

Note: the process for receipt of goods into the wholesale or manufacturing facility involves the performance of certain GMP and GDP-related 'goods-in' activities. In recognition of the above, the date of receipt may be regarded as the date on which the goods were formally receipted onto the company's stock management system, as long as no sales of the product can occur before this. However, if this date is more than two calendar days after the date of actual receipt of the goods into the facility, the 'date of receipt' for the purposes of this notification scheme should be regarded as the date of actual receipt. Please see Table 1 below for examples.

Table 1: Date of receipt

DATE GOODS ENTER THE FACILITY	DATE GOODS ARE RECEIPTED ONTO COMPANY'S STOCK MANAGEMENT SYSTEM	DATE OF RECEIPT FOR PURPOSES OF NOTIFICATION
Tuesday 12 February	Friday 15 February	Tuesday 12 February
Tuesday 12 February	Thursday 14 February	Thursday 14 February
Friday 15 February	Tuesday 19 February	Friday 15 February

Sheet 4: Manufacturer/supplier information

Manufacturer/supplier (mandatory): select either 'manufacturer' or 'supplier' from the drop-down menu.

Name and address of manufacturer and supplier (mandatory): enter the name and address of the manufacturer of the exempt medicinal product in the form in which it was received, and if

the person or company who supplied the product to the notifying company is not the manufacturer, the name and address of that supplier must also be submitted.

Sheet 5: Customer information

Customer code (non-mandatory): the code which the wholesaler or manufacturer uses to identify the customer to whom the exempt medicinal product has been supplied.

Name and address of customer (non-mandatory): the name and address of the customer.

APPENDIX II IN WHICH SITUATIONS SHOULD NOTIFICATIONS BE SENT TO THE HPRA?

	ACTIVITY	NOTIFY DETAILS TO HPRA? (YES/NO)
1	Irish wholesaler sourcing an exempt medicinal product from within the EEA	Yes
2	Irish wholesaler sourcing an exempt medicinal product from an Irish manufacturer, with the following exceptions: a) Exempt products which have been imported from outside the EEA by an Irish manufacturer – the obligation to notify these to the HPRA lies with the Irish manufacturer; b) Exempt products compounded by holders of Irish manufacturers' authorisations – these do not require notification.	Yes No No
3	Holder of an Irish manufacturer's authorisation supplying an exempt medicinal product, which it has manufactured, to an Irish wholesaler for onward supply	No, as the wholesaler is expected to make the notification to the HPRA (as per 2 above)
4	Holder of an Irish manufacturer's authorisation supplying an exempt medicinal product, which it has manufactured, to an Irish pharmacy or medical/dental practitioner	No
5	Holder of an Irish manufacturer's authorisation that distributes an exempt medicinal product which it has compounded under its manufacturing authorisation	No. However, the manufacturer is required to submit a list of unauthorised medicinal products used as ingredients.
6	Irish wholesaler that receives an exempt medicinal product which has been compounded by an authorised manufacturer based outside Ireland but within the EEA	Yes, notification of all details required
7	Non-Irish wholesaler which supplies exempt medicinal product to an Irish pharmacy or practitioner	Not mandatory, but notification is strongly encouraged and will be accepted by the HPRA
8	Holder of an Irish manufacturer's authorisation importing an exempt medicinal product from outside the EEA	Yes
9	Irish wholesaler that receives exempt medicinal product from another Irish wholesaler	No, as the notification to the HPRA will already

	ACTIVITY	NOTIFY DETAILS TO HPRA? (YES/NO)
		have been submitted by the wholesaler that received the product directly from an Irish manufacturer or from another EEA state
10	Irish wholesaler that receives unauthorised product for onward supply to another EEA state or for export to a non-EEA state	No