



IRISH MEDICINES BOARD  
**Guidance Note for the Notification System for Exempt  
Medicinal Products**

**IND-016-01**  
**FEBRUARY 2008**

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

## **CONTENTS**

<b>1.</b>	<b>SCOPE</b>	<b>1</b>
<b>2.</b>	<b>INTRODUCTION</b>	<b>1</b>
<b>3.</b>	<b>GENERAL REQUIREMENTS</b>	<b>2</b>
<b>4.</b>	<b>REQUIREMENTS SPECIFIC TO COMPOUNDED MEDICINAL PRODUCTS</b>	<b>2</b>
<b>5.</b>	<b>NOTIFICATION SYSTEM FOR EXEMPT MEDICINAL PRODUCTS</b>	<b>3</b>
<b>6.</b>	<b>PHARMACOVIGILANCE REQUIREMENTS</b>	<b>8</b>
<b>7.</b>	<b>REPORTING OF SUSPECTED QUALITY DEFECTS</b>	<b>9</b>
<b>8.</b>	<b>FEES</b>	<b>9</b>

## 1. SCOPE

This guidance note describes the system for notification to the Irish Medicines Board of the receipt or importation of exempt (unauthorised) medicinal products that are intended to be supplied in Ireland for human use.

This Notification System applies principally to wholesalers and manufacturers that receive or import, respectively, exempt medicinal products.

## 2. INTRODUCTION

Subject to certain exemptions, medicinal products which are placed on the Irish market are required to have a Product Authorisation issued by the IMB (reflected by a PA number) or, in the case of centrally authorised 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. 538/2007

Medicinal Products (Control of Manufacture) Regulations 2007 S.I. 539/2007

Medicinal Products (Control of Placing on the Market) Regulations 2007 S.I. 540/2007

An ‘exempt medicinal product’ is defined as “a medicinal product to which paragraph 2 of Schedule 1 to 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 his individual patients under his direct personal responsibility.

### **3. GENERAL REQUIREMENTS**

Wholesale authorisation holders 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 third countries (i.e. countries outside of the EEA). Note that both types of authorisation must have this type of activity specified.

Wholesalers and manufacturers which 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 IMB Inspectors during an inspection.

It is essential that all healthcare professionals in the supply chain are aware that exempt medicinal products have not been assessed by the IMB against the criteria of safety, quality and efficacy, and that the responsibility for the clinical use of such products lies with the prescriber.

### **4. REQUIREMENTS SPECIFIC TO COMPOUNDED MEDICINAL PRODUCTS**

Examples of compounded products are patient-specific sterile preparations of cytotoxics, analgesics, antibiotics or parenteral nutrition. Holders of Manufacturer’s Authorisations issued by the IMB 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 section 5 below.

Wholesalers supplying exempt products which are compounded by the holders of Irish Manufacturer’s Authorisations are not required to notify the supply of these products to the IMB.

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

## 5. NOTIFICATION SYSTEM FOR EXEMPT MEDICINAL PRODUCTS

The above-mentioned Regulations (SI 538/2007 and SI 539/2007) require wholesalers and manufacturers which receive or import, respectively, exempt medicinal products to notify the Irish Medicines Board of their receipt. The details listed in stepwise fashion below are required in such notifications.

From February 18th 2008, the notification is required within 7 days of receipt / importation of a consignment of an exempt medicinal product.

From January 1<sup>st</sup> 2009, the notification will be required within 2 working days of receipt of such consignment and will have to be communicated to the IMB electronically. When the notified information is received by the IMB, it will be validated for compliance with the Regulations, and will be returned if any mandatory fields are incomplete. When received and validated, an acknowledgement will be issued to the notifying wholesaler or manufacturer by the IMB.

Wholesalers which receive unauthorised medicinal products from other EEA Member States and distribute these products to the Irish market via other wholesalers are required to adhere to the requirements for notification of sourcing of exempt medicinal products to the IMB.

The requirement to notify the IMB applies only to receipt of “exempt” medicinal products. Therefore, the receipt of unauthorised medicinal product for onward export to other markets (both to EEA and third countries) does not need to be notified to the IMB.

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 IMB of the receipt of the product to be supplied in Ireland as “exempt” as described above.

Holders of Irish Manufacturer’s Authorisations which manufacture and supply unauthorised compounded products are not required to notify details of every product supplied. From February 18th 2008 onwards such manufacturers are required to notify the IMB with details of any unauthorised medicinal products that are used as starting materials (i.e. each product name, active substance(s) and the name of the manufacturer). Regular updates are required if there are any changes to these starting materials.

Notification is not a statutory requirement for non-Irish wholesalers and manufacturers. However, it would be of considerable benefit to patient safety for the IMB to receive from non-Irish wholesalers and manufacturers, details of exempt medicinal products which are sent directly to pharmacists and practitioners in Ireland.

Table 1 overleaf shows the situations in which exempt medicinal product notifications must be made to the IMB and clarifies some areas in which notification is not required.

**Table 1: In which situations should Notifications be sent to the IMB?**

	<b>Activity</b>	<b>Notify details to IMB? Yes / No</b>
1	<b>Irish wholesaler</b> which sources an exempt medicinal product from within the EEA	Yes
2	<b>Irish wholesaler</b> which sources an exempt medicinal product from an Irish manufacturer, with the exception of exempt products compounded by holders of Irish manufacturers' authorisations	Yes
3	<b>Holder of an Irish Manufacturer's Authorisation</b> 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 IMB (as per 2 above)
4	<b>Holder of an Irish Manufacturer's Authorisation</b> which 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 starting materials
5	<b>Irish wholesaler</b> which receives an exempt medicinal product which has been compounded by an authorised Manufacturer based outside Ireland	Yes, notification of all details required
6	<b>Non-Irish wholesaler</b> which supplies exempt medicinal product to an Irish pharmacy or practitioner	Not mandatory, but notification is strongly encouraged and will be accepted by the IMB
8	<b>Holder of an Irish Manufacturer's Authorisation</b> importing an exempt medicinal product from outside the EEA	Yes
9	<b>Irish wholesaler</b> which receives exempt medicinal product from another Irish wholesaler	No, as the notification to the IMB will already have been submitted by the wholesaler which received the product directly from an Irish manufacturer or from another EEA State
1 1	<b>Irish wholesaler</b> which receives unauthorised product for onward supply to another EEA State or for export to a non-EEA State	No

The Notification process is as follows:

### **Step 1: Registration**

Each wholesaler/ 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/ manufacturer intending to submit exempt medicinal product notifications to the IMB)
- Its full mailing Address
- Its Manufacturing or Wholesaler's Authorisation Number
- A Contact person's name, email address and phone number

Once received, an account will be set up by the IMB for that company and an email with a username, password and company code required to access the notification system will be provided.

### **Step 2: Notification Spreadsheet**

The information to be notified (as detailed below) can be entered into a pre-formatted spreadsheet or XML file. A sample spreadsheet and XML file (including XSD definition) are included as part of this guide. The structure of this spreadsheet can be seen in the attachment. It is not possible for the IMB to accept the information in any alternate format.

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

ABCD\_ddmmyyy.xls

where ABCD represents the company registration number for the exempt medicinal product notification scheme, and where ddmmyyy 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 the 1<sup>st</sup> March 2008 then the file should be named *1234\_01032008.xls*.

Once received, an automated email 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 email will be sent to the notifying wholesaler / manufacturer, confirming either the validity of the notification, or requesting that the details are resubmitted with all fields complete.

The spreadsheet is separated into five worksheets as follows:

#### **Sheet 1 – Product information:**

**Notifying Company Code (mandatory):** this is the code which will be provided by the IMB 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.

**Strength and unit (mandatory):** this is the strength of the product, followed by the unit of measurement for that strength (examples are:

- a) “2mg/ml” for an injectable solution
- b) “100mg/5ml” for an oral suspension containing 100mg per 5 ml spoonful
- c) “250mg per 24 hours” for a transdermal patch
- d) “1g/ml” for an injectable solution

When entering products which have more than one active constituent, the combined strength should be entered.

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:

- tablets
- capsules,
- oral suspension,
- powder for solution for injection,
- suppositories)

**Pack size (mandatory):** examples are:

- a) “10 x 5ml”, for a pack containing ten 5ml ampoules of injectable solution
- b) “1 x 150ml”, for a pack containing one 150ml bottle of oral liquid
- c) “1 x 28”, for a pack of 28 capsules
- d) “1x1”, for a pack containing one implant
- e) “1 x 2 fl oz.”, for a pack containing one bottle of sub-lingual liquid

**Number of packs (mandatory):** the number of packs sourced (examples are:

- a) “6” packs of the above-mentioned injectable solution
- b) “1” pack of the above-mentioned oral liquid
- c) “30” packs of the above-mentioned capsules
- d) “3” packs of the above-mentioned implant
- e) “1” pack of the above-mentioned sub-lingual liquid, etc.)

**Trading style (mandatory):** enter the trading style (i.e. the company which markets the product). In the case of products which are 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. The batch number is also requested on sheet 5 if entering customer information (which is non-mandatory).

**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: 11/09” should be entered as “11/2009”;  
 “Use before: Nov 09” should be entered as “Nov 2009”.

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

Note: The IMB recognises that the receipting process for goods received into the wholesale or manufacturing facility involves performing 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 the goods are receipted onto the company’s stock management system. However, if this date is more than two calendar days after the date of actual receipt (i.e. the date of the physical entry) of the goods into the facility, the “date of receipt” for the purposes of this notification scheme should be regarded as the date of the actual receipt (i.e. entry) of the goods into the facility. Please see Table 2 (overleaf) for examples.

**Table 2: Date of receipt**

<b>Date goods enter the facility</b>	<b>Date goods are receipted onto company’s stock management system</b>	<b>Date of Receipt for purposes of Notification System</b>
Tuesday, February 12th	Friday February 15th	Tuesday, February 12th
Tuesday, February 12th	Thursday February 14th	Thursday, February 14th
Friday, February 15th	Tuesday February 19th	Friday, February 15th

#### **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 manufacturer of the exempt medicinal product in the form in which it was received, and if the person/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 which the exempt medicinal product has been supplied.

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

## **6. PHARMACOVIGILANCE REQUIREMENTS**

In accordance with Schedule 2 of S.I. 538 of 2007, the wholesale authorisation holder shall make and maintain written records relating to details of any suspected adverse reaction to a product sold or supplied, of which he/she becomes aware.

In order to meet this obligation, the wholesale authorisation holder 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. Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human use include guidance on pharmacovigilance system requirements and expedited reporting requirements, as well as information on reporting criteria. Systems and procedures developed to meet adverse reaction recording and reporting requirements should be based on this guidance, particularly Part I, chapters 2, 4 and 5 and Part III. This guidance is available from the EU Commission with links available from the IMB website ([www.imb.ie](http://www.imb.ie)), under the headings, Human Medicines, Drug Safety/Companies/Pharmacovigilance Reporting Requirements.

It is important to note that the monitoring system established and maintained should ensure training of all staff in the procedures in place to receive and record adverse reaction reports, as they may be notified through a variety of sources. Once a report has been received, which includes, as a minimum, information on an identifiable patient (i.e. initials/record number/sex/age criteria), a suspected exempt medicinal product and a suspected reaction), it should be reviewed and recorded in an appropriate format by the wholesale authorisation holder.

All such reports should then be submitted to the Pharmacovigilance Section of the IMB, within 15 days of first notification to the wholesale authorisation holder either electronically as described in Part III of Volume 9A of the Rules Governing Medicinal Products in the European Union, or on a CIOMS form (Appendix X). Full contact information for the original reporter, healthcare professional or patient should be included on all reports submitted to facilitate IMB follow-up of cases, as necessary.

In summary, the wholesaler or manufacturer should ensure that a clearly defined process is in place to capture and record any adverse reaction notified, to ensure that any such notification is brought immediately to the attention of a designated senior person and that he / she reports it without delay to the IMB. All relevant personnel should be trained in the procedure.

## **7. REPORTING OF SUSPECTED QUALITY DEFECTS**

SI 539/2007 requires wholesalers who sell or supply exempt medicinal products to inform the IMB of any suspected quality defect which comes to their attention, relating to an exempt medicinal product sourced by them. The regulations also require wholesalers to maintain written records of the details of any suspected quality defects relating to exempt products sold or supplied by them.

Similarly, SI 538/2007 requires manufacturers who manufacture or import exempt medicinal products to inform the IMB of any suspected quality defect which comes to their attention, relating to exempt medicinal products manufactured or imported by them. The regulations also require manufacturers to maintain written records of details of any suspected quality defects relating to exempt products sold or supplied by them.

Details of how to report suspected quality defects to the IMB are available on the IMB website ([www.imb.ie](http://www.imb.ie)). An on-line reporting mechanism is also available via that website.

## **8. FEES**

It is intended to undertake a second consultation with wholesalers and manufacturers on the fee structure for the Notification System for 2008. This Guidance Note will be updated when the fee structure has been finalised.