

Guide to Parallel Imports of Human Medicines



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DEFINITIONS

Parallel importation

The importation from an EU Member State, or an EEA country, of a medicinal product which is equivalent to one already authorised on the Irish market, by an importer who is someone other than the importer appointed by the marketing authorisation holder (MAH) of the product on the Irish market.

Parallel distribution

The marketing of a centrally-authorized product, placed originally on the market in one Member State by the MAH, in any other part of the Community by a 'parallel distributor', independent of the MAH.

Irish-market product

A medicinal product which is the subject of a marketing authorisation in Ireland.

Source country

The EU/EEA country from which the parallel product is imported.

Repackaging

Repackaging includes relabelling and reboxing.

ABBREVIATIONS

DPR	Dual Pack import Registration
EEA	European Economic Area (EU and Norway, Iceland, Liechtenstein)
EMA	European Medicines Agency
EU	European Union
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HPRA	Health Products Regulatory Authority
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PPA	Parallel Product Authorisation
QRD	Quality Review of Documents
SmPC	Summary of Product Characteristics

1 SCOPE

This guide applies to nationally-authorized products which are parallel-imported from another EU Member State or another EEA country and distributed on the Irish market. In order to legally place such a product on the Irish market a parallel import licence is required and the HPRA operates two schemes in this regard. Where the product to be imported differs in any respect from that on the Irish market, a parallel import licence (termed a 'parallel product authorisation') must be obtained; see section 2 below. 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 parallel import licence (termed a Dual Pack import Registration (DPR)) is required; see section 3 below.

The framework for these schemes is that set out in *Commission Communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted* (COM(2003) 839). The simplified procedures in this guide are in accordance with the procedure in the Commission Communication in terms of the information required to be submitted by applicants and the administrative steps to be taken by the HPRA.

The application forms mentioned in this guide are available on the 'Publications and Forms' section of www.hpra.ie.

Products which are centrally-authorized by the European Commission are **not** covered by this guide. Importers wishing to parallel distribute these products must notify the EMA of their intention. Details of the notification system are available on the EMA website. Please note that applicants are required to make all related documentation (including approval letters) received from the EMA available to the HPRA during an inspection.

2 PARALLEL IMPORT LICENCE – PARALLEL PRODUCT AUTHORISATION

2.1 General provisions

A medicinal product originally placed on the market in another EU Member State or EEA country may be parallel imported to Ireland, provided that the equivalent product is already on the market here or has been withdrawn for commercial reasons only, and the importer has obtained a parallel import licence (i.e. parallel product authorisation) from the HPRA to place the parallel imported product on the Irish market. Authorisation is granted under the Medicinal Products (Control of Placing on the Market) Regulations 2007. The parallel import licence is termed a Parallel Product Authorisation and is identified by the letters 'PPA' in front of the authorisation number.

Article 76.3 of Directive 2001/83/EC requires the distributor of a product imported from another Member State to notify his intention to import the product to the MAH and the competent authority in the Member State to which the product is to be imported. For parallel importation

to Ireland, this means informing the HPRA and the MA holder of the Irish-market product. The obligation to inform the HPRA is met by the procedure laid down in this section for submission of an application for a PPA.

In granting a PPA, the HPRA does not consider, and is not in a position to consider, whether any aspect of the authorisation infringes any private civil rights of third parties. The granting of a PPA does not absolve the holder from the need to comply with trademark rights of third parties and, to prevent possible infringements of trademarks, applicants should ensure that they are entitled to use the name in question.

2.2 Conditions of authorisation

A PPA is granted only for a product that fulfils the following criteria:

- The Irish-market product must have a current, full marketing authorisation at the time of submission or, if not still authorised, it must have been withdrawn for commercial reasons only. Where there is no longer a marketing authorisation on the Irish market (withdrawn for commercial reasons), the product information published on the MRI Product Index at www.hma.eu, which is current and available, should be used by the PPA holder.
- The parallel-imported product must have the same active substance(s), the same pharmaceutical form and be identical to, or have no significant therapeutic difference from, the Irish-market product.
- The parallel-imported product must be imported from an EU Member State or an EEA country and it must have a current, full marketing authorisation in that country.
- The parallel importer must demonstrate how the aims of any additional risk minimisation measures imposed on the Irish market product, e.g. a patient alert card or supply through a controlled distribution system, will be achieved for the parallel imported product. The parallel importer should liaise with the Irish market MAH and/or the HPRA to discuss these requirements where they apply.

A PPA may be granted for a parallel-imported product from one or more source countries. Where particulars concerning the product (such as appearance or excipients) differ between source countries, the differences are stated in the authorisation document.

A PPA is granted either for unlimited validity or, if deemed necessary for pharmacovigilance reasons, for a maximum period of five years, at which time the authorisation must be renewed. After the renewal, the PPA remains valid indefinitely.

In accordance with the European Court of Justice judgement in C-172/00, a parallel import licence may be granted or may remain in force even where the marketing authorisation for the Irish-market product is withdrawn for commercial reasons or is replaced by a new version under the same or a new MA number, so long as there are no risks to public health. In cases where the Irish-market authorisation is withdrawn and the parallel imported product remains authorised,

the HPRA may request certain information from the parallel importer in order to adequately monitor adverse reactions in Irish patients.

The PPA ceases to be valid if the parallel-imported product ceases to have a valid marketing authorisation in the EU Member State or EEA country from which it is imported.

2.3 Applications

2.3.1 New applications

In order to obtain a PPA, the proposed authorisation holder, or another person acting on behalf, must submit an application as set out below.

An application for a PPA consists of:

- Completed application form 'Application for a Parallel Import Licence'.
- 'Human Medicines Fee Application Form'.
- Covering letter.
- Where a company is proposed as the PPA holder, a Certificate of Incorporation for the company (for the first application only).
- Proposed Summary of Product Characteristics (SmPC). This must be based on the authorised SmPC for the reference product as issued by the HPRA only and no other version will be accepted. All SmPCs are available on the HPRA website at www.hpra.ie.
- Proposed colour label mock-ups for the immediate container and the outer carton.
- Proposed colour mock-up of the package leaflet.
- Braille declaration, as outlined in the 'Guide to Labels and Leaflets of Human Medicines', available on the 'Publications and Forms' section of www.hpra.ie.
- Manufacturer's authorisation for the company responsible for relabelling or repackaging and batch certification of the repackaging activity (if different) issued by the regulatory authority in the appropriate EU Member State, EEA country, or United Kingdom (Northern Ireland) (if the manufacturer is not an Irish company).
- Full colour, high quality scans/photographs of the parallel-imported product, clearly showing all sides of the packaging, the product leaflet and the physical appearance of the product itself. **Applicants are advised that, if scans are not of sufficient quality or clarity, the HPRA retains the right to request a physical sample of the product.**

Applicants should note the requirements outlined in the Commission Communication, particularly the need to give advance notice to the PA holder prior to placing the repackaged product on the market. The European Court of Justice, in C-143/00, suggested a period of 15 working days as a reasonable time for the parallel importer to give notice to the trade mark proprietor by supplying it simultaneously with a sample of the repackaged pharmaceutical product. According to the Commission Communication, in all circumstances repackaging is permitted **only** if it is necessary. Any alleged infringement of intellectual property arising from the repackaging is a matter for the parallel importer and the trademark holder only.

Copies of the application forms, notes for completing the application forms, and fee forms are available from the HPRA website. Information on the fees and the address to which to send the application is given in Appendix 1 and further details on completing the application forms are given in Appendix 2.

Source countries

A number of source countries may be applied for using one application form. Additional countries may also be applied for by variation at a later stage (see below for further details).

Specific Mechanism

Under the Treaties of Accession signed by the EU Member States with the Czech Republic, Estonia, Latvia, Lithuania, Hungary, Poland, Slovakia and Slovenia in 2003, Bulgaria and Romania in 2005 and Croatia in 2012, there is a specific mechanism which entails a temporary derogation to the principle of free movement of pharmaceutical products.

Under the mechanism, the holder, or beneficiary, of a patent or supplementary protection certificate for a pharmaceutical product filed in a Member State at a time when such protection could not be obtained in one of the above-mentioned new Member States for that product, may rely on the rights granted by that patent or supplementary protection certificate in order to prevent the importation and marketing of that product in the Member State or States where the product in question enjoys patent protection or supplementary protection, even if the product was put on the market in that new Member State for the first time by him or with his consent.

Any person intending to import or market a pharmaceutical product covered by the above paragraph in a Member State where the product enjoys patent or supplementary protection, must give one month's notice to the holder or beneficiary of such protection of their intention, prior to submitting the application, and confirm that they have done so in the application regarding that import. The notification must give the holder or beneficiary sufficient information to adequately identify the product concerned and the country of origin.

Determination of whether the specific mechanism is applicable is the responsibility of the applicant. The HPRA is not responsible for such a determination and the granting of a parallel import licence by the HPRA does not constitute confirmation of either the application or non-application of the mechanism.

This mechanism does not apply to Malta or Cyprus.

Validation

Applications are subject to an administrative check on receipt to ensure that all necessary documentation is submitted with the application. Incomplete applications will not be validated until the missing documentation is provided. In certain cases, the application may be returned to the applicant for resubmission. An administrative fee will be charged in such cases.

Assessment of application

Within ten working days of validation, the application is assessed to determine if a presumption of identity is reasonable and if therapeutic equivalence between the imported and Irish product can be reasonably presumed.

If these assumptions can be made, the proposed SmPC, labels and package leaflet are assessed and any queries sent to the parallel importer within 15 working days of validation. The 'clock' is then stopped. On receipt of a response, the clock is restarted and the assessment concluded within 45 working days of validation. The decision on the application is then forwarded to the parallel importer by the HPRA.

If presumptions of identity and therapeutic equivalence cannot be made, the clock is stopped within 10 days of validation in order for the HPRA to seek information from the regulatory authority in the Member State from which the product is to be imported. At the same time, provided the applicant agrees, the MA holder that supplies the Irish market product is contacted and asked to indicate whether or not the product(s) are therapeutically equivalent. On receipt of the necessary information, the clock is restarted and the assessment of the application is continued in accordance with the procedure outlined above.

2.3.2 Variations

The parallel importer should regularly check the product information of the Irish market product, as changes may require a revision of the product information supplied by the importer with the parallel-imported product or other amendments to the parallel import licence. This particularly relates to significant safety variations which must be incorporated into the parallel-imported product information.

There should be systems in place for the parallel importer to ensure that they have obtained the most recent version of the Irish market product for comparison against the imported product. Records of these checks should be maintained.

The parallel importer must also keep informed of any relevant change in the parallel-imported product in order to ensure that the PPA document reflects the current situation at all times. Importers are especially reminded to check the labels and leaflets of the parallel-imported product as changes made to the texts may have consequences for the product information included with the parallel-imported product. Should the parallel-imported product's labels and leaflets not be in English, then the importer should be able to show proof of translation.

Importers are also reminded that, when the marketing authorisation number is not found on the outer label of the parallel-imported product, it is necessary to check the source country regulatory authority website to ensure that the correct marketing authorisation number is registered.

For marketed products, a full review of all the product information (parallel-imported product and Irish-market product) should be carried out on a quarterly basis at a minimum. For non-marketed products a bi-annual review of the product information is sufficient. All changes must be submitted by variation.

All variations must be approved by the HPRA **prior to implementation** by the parallel importer. Applications should be made using the 'Application for a Variation to a Parallel Import Licence' form, available in the 'Publications and Forms' section of www.hpra.ie, which indicates the variation classification (Type IA or Type IB) and category for each type of change. Additional guidance on the documentation to be submitted in support of each category of change is provided in Appendix 3.

2.3.3 Additional source countries

Additional source countries may be added to the PPA. Applications for additional countries should be made using the form 'Application for Addition of a Source Country to a Parallel Import Licence'.

Applications for additional source countries are processed according to the same procedure and timelines as new PPA applications. Applicants should ensure that the product information (SmPC, labels and patient leaflet) is correct and in line with the reference product prior to submission of the additional source country variation.

2.3.4 Renewals

The initial PPA remains in force either indefinitely or for a maximum of five years (see section 2.2). If a five-year authorisation is given, it must be renewed at least once if the holder wishes to continue parallel importation of the product. An application for renewal must be made not later than six months before the date of expiry of the authorisation, using the form 'Application for Renewal of a Parallel Import Licence'. The PPA holder should consult the HPRA 'Guide to Renewal of Marketing Authorisations – Human Medicines' for general guidance on updating the SmPC, labels and package leaflet at renewal.

After the renewal, the PPA remains valid indefinitely.

2.3.5 Withdrawal of PPA

If the PPA is to be withdrawn, the holder of the authorisation should notify the HPRA using the form, 'Notification of Withdrawal of Authorisations or Certificates for Human Medicines'. Guidance on withdrawals is available in the document 'Guide to Withdrawal of Authorisations or Certificates for Human Medicines'.

2.4 Product information

2.4.1 Summary of Product Characteristics (SmPC)

A reduced SmPC should be provided for each pharmaceutical form and strength in a parallel imported product range. Guidance on the content of the SmPC is provided as a template in Appendix 4. Additional guidance on specific sections of the SmPC is also given below, using the numbering of the SmPC. Reference to the SmPC of the Irish market product will be made on the HPRA website. Please also refer to the QRD product information template, which can be found on the Product Information Templates page of the EMA website.

1. Name of the medicinal product

The name should be given in the order: (invented) name, strength and pharmaceutical form; the same name must also be used in the leaflet and on the labels.

In order to minimise confusion on the market, the name of the Irish market product should be used as the name for the parallel imported product. However, in cases where this is not possible (e.g. for trademark reasons), the PPA holder may propose to use either the trade name of the source country product or a generic name provided that the proposed name is in line with the HPRA 'Guide to Invented Names of Human Medicines'. For example, the use of the trade name of the source country product will only be accepted if the HPRA is satisfied that that name is appropriate with respect to the general principles outlined in the above guideline. The use of a generic name for a parallel imported product will not be accepted for prolonged-release products and will only be accepted where the HPRA is satisfied that the parallel imported product is therapeutically equivalent to the Irish reference product.

2. Qualitative and quantitative composition

The qualitative and quantitative declaration of the active substance should be included, along with the standard statement 'For the full list of excipients, see section 6.1'.

Where a product contains excipients, knowledge of which is essential for the proper administration of the medicinal product, a statement that the product contains these excipients should be included in this section, followed by the standard statement 'For the full list of excipients, see section 6.1'. See also the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) as published on the website of the European Commission in the Notice to Applicants, Volume 2C.

3. Pharmaceutical form

Product parallel imported from more than one Member State may differ in appearance. The appearance of the product should be described, with reference to the Member State from which the product is to be parallel imported.

4. Clinical particulars

Where an excipient with a recognised action or effect is declared on the label, the relevant warning must be included in the SmPC, in section 4.3, 4.4 or 4.8 as appropriate.

6.1 List of excipients

The list of excipients is usually available from the package leaflet of the product on the market in the source country.

Where a product is imported from more than one Member State, a single list of excipients should be given if the excipients in the product parallel imported from all Member States concerned are the same. If there are differences in one or more excipients, separate lists should be given, related to the Member State from which the product is to be parallel imported. Each excipient list should have the heading 'Product as sourced from <source country>'. The presence of certain excipients in a parallel imported product, if different from those present in the Irish reference product with the same product name, may not be acceptable, due to the risk of severe allergic reactions. An example of such an excipient is soya oil.

For clarity, it is recommended that each excipient be listed on a separate line.

6.2 Incompatibilities

One of the following standard statements should be used where appropriate:

- Not applicable. (*E.g. for solid oral pharmaceutical forms.*)
- In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. (*E.g. for parenterals.*)
- This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. (*E.g. for parenterals.*)

6.3 Shelf life

Batches of parallel imported product placed on the market in Ireland must keep the same expiry date as they had in the country from which they are imported. The importer is not permitted to change the expiry date.

The statement that should be included in this section is 'The shelf life expiry date of this product is the date shown on the container¹ and outer carton of the product as marketed in the country of origin'.

(Where the parallel imported product is repackaged into another container, the importer must justify retaining the same shelf life.)

A reference to the in-use shelf life should be included if appropriate. In cases where the in-use shelf life of the Irish market product is different than that on the container of the parallel imported product, the in-use shelf life proposed by the applicant should be the more conservative of the two.

6.4 Special precautions for storage

The storage statements on the label of the Irish market product may be different from those on the container of the parallel imported product. The storage statements proposed by the applicant should be the more conservative of the two.

6.5 Nature and contents of container

All pack sizes to be imported should be included.

6.6 Special precautions for disposal <and other handling>

One of the following standard statements should be used when appropriate:

- No special requirements. (E.g. for solid oral pharmaceutical forms.)
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements. (E.g. for cytotoxics.)

2.4.2 Labels

Parallel imported products should be labelled with the following information:

- name of the product
- the PPA holder's name and address
- the PPA number
- other details as may be necessary to comply with Directive 2001/83/EC and the European Commission guidelines on 'Excipients in the labelling and package leaflet of medicinal products for human use' and on 'readability of the labelling and package leaflet of medicinal products for human use'
- the name and address of the manufacturer of the product

¹ The actual name of the container should be used (e.g. bottle, blister, etc.).

- the batch number/packaging code associated with the repackaging/relabelling operation carried out on behalf of the parallel importer

If some of the required label text is already on the parallel imported product in English, these items do not have to be repeated on the importer's label.

The PPA holder's label text may be placed over foreign language text. If the information already printed on the container or carton differs from the information the holder is required to include on the label (e.g. different storage conditions, different product name), the original text must be completely and effectively covered by an over-label.

Parallel imported products must comply with the requirements of Directive 2001/83/EC in respect of Braille; existing Braille on the imported product may be used, provided it complies with these requirements. Otherwise, the existing Braille must be obscured and new Braille text must be applied. Further guidance on Braille requirements is available in the HPRA 'Guide to Labels and Leaflets of Human Medicines', available in the 'Publications and Forms' section of www.hpra.ie.

If the parallel imported product is known to contain any excipient that has a recognised action or effect as defined by the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the PPA holder is required to label the parallel imported product with this information. Country-specific label text may be needed if the excipients to be declared on the label differ depending on the Member State from which the product is imported or if excipients are known for product imported from some Member States but not from others.

The label must also identify the manufacturer of the product in the relevant source country.

Each application (whether for a new PPA, a renewal, to add an additional source country or for a variation that affects the label) must be accompanied by full colour mock-ups of the labels. The mock-ups should show the placement of the PPA holder's label on the outer packaging and immediate container. The position of the over-label on the carton/container must not be changed without approval from the HPRA.

The HPRA has identified some minor amendments to the labelling and package leaflet which are not considered to require formal assessment. PPA holders are advised that the following changes do not require notification to the HPRA:

- Moving the location of the batch number/packaging code/expiry date on outer packaging, provided that no other details are changed.
- Transfer of the entire text of a carton face to an opposing face, with no change to text, font size, layout, appearance or readability of the text. Please note that a change in the position of an over-label requires approval from the HPRA.

- The introduction of, or any change to, a barcode, e.g. the number on the barcode, that does not affect any other aspect of the labelling and does not change the location of the barcode, or the position or size of an over-label if applicable.
- Change to printing key lines on package leaflet or labelling, with no change to text, font size, appearance or readability of information.
- Change in the dimensions of the patient information leaflet resulting in an increase in the font size of the text.
- Change to the dimensions of a carton with no change in layout or font size of the text.
- Relocation of Braille (with no change to the Braille text, the text or the position of any other over-labels).
- Change to a packaging code/internal reference code (not the internal batch number) on the packaging.
- Change to the size, colour or font of a company logo or trademark on a carton that is similar in size to the currently approved logo/trademark and does not interfere with the legibility of the required text.
- Addition of a quick response (QR) code or 2D barcode to product labelling and/or package leaflets for internal control purposes or anti-counterfeit measures, with no addition or impact to the approved product information and provided that the conditions as outlined in section 9.7 of the HPRA 'Guide to Labels and Leaflets of Human Medicines' and the safety features labelling requirements outlined below are met.
- Changing from over-labelling to over-printing on the immediate packaging, provided both options have been approved during the initial authorisation.

In such instances, the revised labels or patient leaflet should be submitted to the HPRA at the next regulatory activity involving a change in the product information. Any and all other changes to product labels or package leaflets will continue to require a formal notification to the HPRA.

Labelling of oral contraceptives

Where the Irish product is presented in calendar packs listing the days of the week on the blister, the blisters for the proposed parallel-imported product must also list the days of the week in English on the blisters. This is due to the potentially significant clinical consequences of either failing to take the correct tablet on a given day or inadvertently taking two tablets on the same day.

Safety features

In accordance with the *CMDh implementation plan for the introduction of the safety features on the packaging of nationally authorised medicinal products for human use (CMDh/345/2016)*, a unique identifier (UI) carried by a 2-D barcode and an anti-tampering device (ATD) is required on the packaging of prescription medicines and certain non-prescription medicines for the purposes of authentication and identification.

The PPA holder must ensure the authenticity of the manufacturer's unique identifier and the integrity of the anti-tampering device. Where safety features are required to be applied on the packaging of a medicinal product in line with the Falsified Medicines Directive (Directive

2011/62/EU), it must be ensured during the repackaging operation that the repackaged product will carry appropriate safety features.

In line with the Commission Delegated Regulation (EU) 2016/161, where a repackaging operation occurs, the PPA holder must ensure that the unique identifier applied by the original manufacturer is decommissioned and replaced by an equivalent unique identifier as part of the repackaging operation.

The PPA holder must ensure that the unique identifier placed on the packaging complies with the requirements outlined in the HPRA 'Guide to Labels and Leaflets of Human Medicines'. The PPA holder must also ensure that the required data elements are included on the packaging in human-readable format.

As part of the repackaging operation, if the anti-tampering device applied by the original manufacturer is no longer intact, it must be replaced. The PPA holder must ensure that the repackaged medicinal product has an appropriate anti-tampering device, i.e. one that allows verification that the packaging of the product has not been tampered with.

2.4.3 Package leaflet

Leaflets should be drawn up in accordance with Directive 2001/83/EC, the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' and on 'Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use'. Additional guidance for leaflets for parallel imported products is given below.

Product name

To overcome potential confusion for patients when parallel imports have a different product name to the Irish product, the following statement should be included in the package leaflet: '*The name of this product in <source country> is ...*'. Please also refer to section 2.4.1 above.

Clinical details

The leaflet of the parallel product should use the same wording as that contained within the package leaflet of the Irish market product.

Excipients

The excipients in the parallel imported product are usually given in the package leaflet of the product on the market in the source country.

- A single list of excipients should be given if the excipients in the parallel imported product from all Member States are the same.
- If there are differences in the excipients in the product coming from a number of source countries, separate lists should be given, related to the Member State from which the product is to be imported. However, it should be noted that if the compositions vary

significantly, country-specific leaflets may be needed for these parallel imported products to avoid confusion.

Where a known excipient with a recognised action or effect is declared on the label, the relevant warning must be included in the leaflet, in the section which gives the list of information necessary before taking the medicinal product.

Manufacturer

The manufacturer(s) of the product intended to be parallel-imported (as defined by Directive 2001/83/EC) is/are normally named in the package leaflet of the product on the market in the source country. Where the manufacturer does not appear in the source country package leaflet, the parallel importer can source this information from the source country regulatory authority.

The manufacturer(s), as listed in the package leaflet on the market in the source country, must be listed in the package leaflet to be supplied with the parallel-imported product when placed on the market in Ireland. Where a number of source countries are involved and the manufacturing sites are different, the name and address of each manufacturer should be listed in the package leaflet.

Where a combined leaflet is used and where different manufacturing sites are responsible for the manufacture of the different strengths, the manufacturer(s) and the corresponding strength(s) must be listed in section 6.

Number of leaflets

One leaflet may be sufficient for a parallel-imported product sourced from a number of Member States if there are only minor differences in the information to be included in the leaflet. However, it may be necessary to provide more than one leaflet if the information differs between the parallel-imported products on the market in different Member States to an extent which could be confusing to patients. The applicant should prepare the leaflet(s) carefully, bearing in mind the requirement of Directive 2001/83/EC that 'the package leaflet should be written in clear and understandable terms for the patient...' In particular, the section on excipients should be laid out in a manner which makes it succinct, readable and patient-friendly.

Where more than one leaflet is necessary, it is the responsibility of the PPA holder to ensure that the correct leaflet is included with each batch, in accordance with the requirements of Good Manufacturing Practice.

Full colour mock-ups of the leaflet are required to accompany each application for a new PPA, an additional source country, a variation which affects the leaflet, or a renewal. Compliance with the provisions of Directive 2001/83/EC, article 56a is also mandatory. The package leaflet should be available on request for partially-sighted people in a suitable print, taking into consideration all aspects determining the readability (e.g. font size (sans serif typefaces, 16 - 20 point), contrast (black letters on white paper), word spacing, text alignment, line spacing, layout, paper quality). For blind people, the text has to be provided in an

appropriate format. It is recommended to provide the text in a format perceptible by hearing (CD-ROM, audiocassette, etc.).

2.5 Manufacture, batch control and wholesale

2.5.1 Batch control and batch testing

In regard to the necessary batch control documentation that must accompany products moved from one Member State to another, it is intended that, wherever possible, a presumption of conformity with the specifications of the parallel-imported product will be made.

In instances where it is impractical to make this presumption, or where special problems exist, the parallel importer may be required to provide proof of conformity by means other than by documents to which he has no access. This may involve testing of each batch of the parallel-imported product by the parallel importer.

Where the HPRA requires the parallel-imported product to be tested by the parallel importer, details will be required on the following:

- the test methods and specification limits,
- analytical method validation data where appropriate,
- the name and address of the manufacturer responsible for testing and for batch release, and documentary evidence that the manufacturer is appropriately licensed,
- the name and address of the testing laboratory (if not part of the manufacturer responsible for batch release) and documentary evidence that the laboratory is approved by the relevant competent authority.

2.5.2 Manufacturers' authorisations

Labelling and repackaging are defined as manufacturing operations and the parallel importer or other company that carries out these operations must hold a manufacturer's authorisation. Manufacturers in Ireland are authorised under the Medicinal Products (Control of Manufacture) Regulations 2007 to 2012. Application forms and information on authorisation requirements may be obtained from the HPRA website or by contacting the Compliance department of the HPRA.

If wholesaling the product in Ireland, a parallel importer who holds a manufacturer's authorisation is exempted from the requirement to hold a wholesaler's authorisation to wholesale parallel-imported products, provided that the products are covered by the manufacturer's authorisation (i.e. the manufacturer has carried out manufacturing activities related to those products).

2.5.3 Wholesalers

Where the parallel importer wholesales the product in Ireland and is not the holder of a manufacturer's authorisation, a wholesaler's authorisation is required under the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 to 2012. Alternatively, any wholesaler within Ireland who is contracted by the parallel importer to carry out the importation and the wholesaling activities on his behalf must be authorised in accordance with the above Regulations. If wholesaling to Ireland takes place from a wholesaler or manufacturer based in another Member State, it must be appropriately authorised by the competent authority of the Member State concerned.

The wholesaler's authorisation must name parallel imported products as a category of medicinal product that may be wholesaled. This may require variation of an existing wholesaler's authorisation to include this category of product. Wholesalers involved in the supply of parallel-imported products must also have appropriate controls in place within the operation's quality system to ensure and maintain continued compliance with the requirements of the PPAs.

Application forms and information on authorisation requirements may be obtained from the HPRA website or by contacting the Compliance department of the HPRA.

2.5.4 Batch recalls

Parallel importers are required to ensure that there is a clear audit trail from the supplier (i.e. authorised manufacturer or wholesaler) in the source country. In the event of a recall of a batch of the parallel imported product in the source country, it is imperative that the importer is informed by their supplier so that the importer can take appropriate action on the Irish market, in conjunction with the HPRA. The HPRA requires there to be a contract/technical agreement in place between the supplier and the importer to ensure that information on recalls is passed to the parallel importer. The contract/technical agreement may be requested for review in the course of HPRA inspections at manufacturers and wholesalers.

Should the marketing authorisation on which the PPA authorisation is based be suspended, revoked or withdrawn for quality, safety or efficacy reasons, a recall of the PPA product may be required to be executed by the PPA authorisation holder.

3 PARALLEL IMPORT LICENCE - DUAL PACK IMPORT REGISTRATION

3.1 Introduction

Where a product that is the subject of a national marketing authorisation and is marketed in another Member State is identical in all respects (including identical packaging, labels and leaflets) to the product on the Irish market, it is termed a 'dual pack'. A dual pack may be placed on the market in Ireland provided that the importer or another person acting on his behalf obtains a registration from the HPRA to parallel-import the product. The registration is termed a Dual Pack import Registration (DPR) and is identified by the letters 'DPR' in front of the registration number as granted by the HPRA. The DPR number must be displayed on the outer carton of each pack. Over-labelling/over-printing requirements in relation to parallel imported packs via the DPR scheme are set out in 3.3 below.

A DPR is granted only for imported products that fulfil all of the following conditions:

- 1 The Irish market product must have a current, full marketing authorisation at the time of DPR application submission.
- 2 The imported product must be identical to the Irish market product in terms of SmPC, outer and inner pack labels, package leaflet and shelf life (as stated on the SmPC, regardless of whether the SmPC is contained within the pack).
Note: minor, editorial differences in the SmPC may be acceptable provided the overall content and substance of the SmPC is the same, e.g. 'Store below 25°C' is equivalent to 'Do not store above 25°C'.
- 3 The imported product must be imported from another EU Member State or EEA country and have a current, full marketing authorisation in that country.
- 4 The applicant provides a declaration that one month's prior written notification has been given by the applicant to the MA holder of his intention to parallel import the product in advance of submitting the DPR application. A copy of the written notification sent to the MA holder must accompany the application submitted to the HPRA. See Appendix 5 for an example of the format to be used for the written notification.

Where the specific mechanism is applicable to the application (see section 2.3.1 above), the applicant also provides a copy of the notification demonstrating that one-month prior notification of the intended import or marketing of the product in Ireland has been given to the holder/holder's beneficiary of a medicinal product patent or supplementary protection certificate.

Determination of whether the specific mechanism is applicable is the responsibility of the applicant. The HPRA is not responsible for such a determination and the granting of a DPR by the HPRA does not constitute confirmation of either the application or non-application of the mechanism.

It is important to highlight that where the MA holder provides a response indicating the non-existence of joint packs between the relevant markets, the product in question is not eligible for registration under the DPR scheme. In such cases an application for a DPR should not be submitted to the HPRA. If an application has already been submitted and/or a DPR granted, the HPRA should be immediately informed and the application or registration withdrawn. If the response from the MA holder includes any other valid objection to the intention to parallel import, a copy of the response should be attached to the application for the DPR.

The registration holder is expected to keep informed of any relevant change in the Irish market product in order to ensure that each consignment of product imported is compliant. It is the expectation of the HPRA that this would be achieved by obtaining a sample (reference) of the Irish market product from the main supply chain in Ireland at least quarterly for visual comparison with the parallel-imported product obtained from the source country. Checks to be performed include a comparison of the outer and inner packaging, leaflet (version number and content) and shelf life (as stated on the SmPC, regardless of whether the SmPC is contained within the pack). These checks should be recorded. There should be a system in place to ensure that the reference pack obtained is the most recent version on the Irish market and is not itself a parallel imported product.

There should be adequate controls in place to ensure that sample (reference) packs do not re-enter the distribution chain and are maintained as records. Similarly, any imported products where the secondary packaging has been opened to access leaflets, etc., may not be placed back into the distribution chain by a wholesaler.

The DPR registration ceases to be valid if any of conditions 1 to 3 above are no longer met and further supply should cease immediately. The HPRA should be informed and the registration withdrawn. At a later date, should the importer be in a position to meet all of the conditions attaching to the DPR scheme, a new application as outlined in 1 to 4 above (including a copy of the new notification to the MAH) must be submitted to the HPRA and a registration must be granted by the HPRA before any importation can begin.

The registration holder should have documented procedures in place describing the implementation and recording of the above requirements. Note that the HPRA may inspect DPR-related procedures at Irish wholesalers and at Irish DPR holder sites prior to the granting of a new DPR (see also 3.2.3 below.)

3.2 Applications

3.2.1 Application documentation

In order to obtain a dual pack import registration, the proposed importer, or another person acting on his behalf, must submit an application as set out below.

An application for a dual pack import registration consists of:

- 'Application Form for Dual Pack Import Registration'
- 'Fee Application Form'
- A mock-up of the over-label showing its intended position on the outer carton. Note that if over-printing is to be used instead of an over-label, a mock-up showing the intended over-printing should be provided.

Important note: the application process is a simplified one and is based on the principle of self-certification. Therefore, prior to applying, particular care should be taken to establish that the product that is intended to be parallel-imported is a true dual pack.

Copies of the application form and fee forms are also available from the HPRA website. Applications can be submitted in hard copy or electronically. Address details are available in Appendix 1.

3.2.2 Validation

Applications are subject to an administrative check on receipt to ensure that all necessary parts of the form are completed and appropriate fees are received. Incomplete applications will not be validated until the complete forms and correct fees are received. In certain cases, the application may be returned to the applicant for resubmission. An administrative fee will be charged in such cases.

3.2.3 Review of application

Each registration application will be reviewed by the HPRA to ensure that the applicant has certified compliance with the terms of the scheme. No assessment of labels and leaflets will be carried out by the HPRA.

3.3 Over-labelling/over-printing of dual packs

Where a DPR has been granted by the HPRA, and prior to the product being placed on the Irish market, the holder of the DPR must ensure that a label is placed, in the same position, on the outer carton of each pack. This label must include the words 'Parallel imported by' followed by the name of the DPR holder and the registration number granted by the HPRA. The label should have a permanent adhesive and should not obscure any of the original text on the pack.

The application form for a DPR requires the applicant to state the site at which the above over-labelling operation will take place, and to provide evidence that this site is appropriately authorised. The label must be applied by an authorised manufacturer of medicinal products (see 3.5.1 below).

In the event that, following the initial registration, the applicant wishes to change the site performing the over-labelling operation, this should be notified to the HPRA and a revised

application form should be provided, accompanied by evidence that the proposed site is appropriately authorised.

Over-printing of packs may be performed instead of over-labelling, provided the quality and legibility of the over-printing on DPR packs are of an acceptable standard.

3.4 Removal from the register

A registration will only remain valid if it complies with the terms of the registration as per the application form. It is the responsibility of the registration holder to inform the HPRA should the situation change post-registration. In this case, a written notification should be submitted to the Receipts and Validation section in order to remove a product from the register.

Changes in the wholesale distributor responsible for the distribution of the DPR product into the Irish market will not necessitate removal of the product from the register. However, such changes must be notified to the Compliance department of the HPRA, to ensure that the distribution operation is appropriately authorised; see also section 3.5.2 below.

The HPRA may also remove a product from the register if it is found to be no longer in compliance with the terms of the registration. In particular, should the authorisation on which the registration is based be suspended, revoked or withdrawn for quality, safety or efficacy reasons, the registration will cease to be valid.

3.5 Manufacture and wholesale

3.5.1 Manufacturer's authorisation

Over-labelling and over-printing are considered a manufacturing operation and the parallel importer or other company that carries out this operation must therefore hold a valid manufacturer's authorisation. Manufacturers in Ireland are authorised under the Medicinal Products (Control of Manufacture) Regulations 2007. Application forms and information on authorisation requirements may be obtained from the HPRA website or by contacting the Compliance department of the HPRA. The manufacturer's authorisation number must be stated in the application form when submitting an application for a DPR registration.

If wholesaling the product in Ireland, a parallel importer who holds a manufacturer's authorisation is exempted from the requirement to hold a wholesaler's authorisation to wholesale parallel-imported products, provided the products are covered by the manufacturer's authorisation (i.e. the manufacturer is authorised to perform secondary packaging activities).

3.5.2 Good Distribution Practice

The applicant is required to confirm that the product(s) will be distributed in accordance with the EU Guidelines on good distribution practice, that detailed distribution records will be kept

which will facilitate the identification of each customer of each batch in the event of a potential recall, and that each batch will be checked for compliance by the Responsible Person or by other personnel designated by the Responsible Person (prior to marketing). This compliance check will include checks against the Irish authorised labels and package leaflet for the product(s) concerned. There should be detailed records of these checks having been performed.

There should be adequate controls in place to ensure that the Irish reference packs do not re-enter the distribution chain and are maintained as records. Neither may any imported products where the secondary packaging has been opened to access leaflets, etc., be placed back into the distribution chain by a wholesaler.

3.5.3 Wholesale authorisations

Where the parallel importer wholesales the product in Ireland and is not the holder of a manufacturer's authorisation, a wholesaler's authorisation is required under the Medicinal Products (Control of Wholesale Distribution) Regulations 2007. Alternatively, any wholesaler in Ireland contracted by the parallel importer to carry out wholesale activities on his behalf must be authorised in accordance with the above Regulations. If wholesale takes place from a wholesaler or manufacturer based in another Member State, that company must be appropriately authorised by the competent authority of the Member State concerned. Technical agreements should be in place between all relevant parties.

The wholesale authorisation must name DPR products as a category of medicinal product that may be wholesaled. This may require variation of an existing wholesaler's authorisation to include this category of product. Wholesalers involved in the distribution of DPR products must also have appropriate controls in place within their quality system to ensure and maintain continued compliance with the requirements of the DPR scheme.

An inspection of the wholesale operation will be required to ensure compliance of the operation with the requirements of the registration scheme. It should be noted any such variation to a wholesaler's authorisation must be completed prior to undertaking of the distribution activity.

Application forms and information on authorisation requirements may be obtained from the HPRA website or by contacting the Compliance department of the HPRA.

3.5.4 Batch recalls

Parallel importers are required to ensure that there is a clear audit trail from the supplier (i.e. authorised distributor or manufacturer) in the source country. In the event of a recall of a batch of the parallel-imported product in the source country, it is imperative that the importer is informed by the supplier so that the importer can take appropriate action, in conjunction with the HPRA. The HPRA requires that there be a contract/technical agreement in place between the supplier and the importer to ensure that information on recalls is passed to the parallel importer. This

contract/technical agreement may be requested for review during the course of inspections of manufacturers and wholesalers.

Should either of the marketing authorisations on which the registration is based be suspended, revoked or withdrawn for quality, safety or efficacy reasons, the registration holder may be required to execute a recall of the product.

3.5.5 Terms of registration compliance

A DPR registration will only remain valid if it complies with the terms of the DPR confirmation letter. In order to confirm that the imported product is identical to the Irish product with an identical SmPC (if contained within the packaging), identical outer and inner packaging labels, identical package leaflet and shelf life, the registration holder should compare the imported packs with packs already on the Irish market at either wholesale or retail level.

APPENDIX 1 FEES AND ADDRESSES FOR THE APPLICATION

A1.1 Fees for applications

Fees are detailed in the latest Health Products Regulatory Authority (Fees) Regulations. These are revised annually and are available from the Government Publications Office. Orders may be emailed to publications@opw.ie.

The HPRA 'Guide to Fees', the 'Fee Application Form' and details on payment are available from the HPRA website. Payment is to be made with the application. Fees are payable to the account of the Health Products Regulatory Authority.

Swift Code: AIBKIE2D

IBAN: IE 54 AIBK 931012 33712185

Allied Irish Bank

1-3 Baggot Street Lower

Dublin 2

Applications should be submitted as per the HPRA 'Guide to Electronic Submissions – Human Medicines'.

A1.2 Address for applications submitted on CD/DVD

Receipts and Validation

Health Products Regulatory Authority

Kevin O'Malley House

Earlsfort Centre

Earlsfort Terrace

Dublin 2

D02 XP77

A1.3 Email address for electronic DPR applications

Scanned signed versions of the application form can be emailed to submissions@hpra.ie.

APPENDIX 2 GUIDANCE ON COMPLETING THE PARALLEL IMPORT LICENCE APPLICATION FORMS

Application form types

There are four forms designed for applications relating to applications for parallel import licence for parallel-imported products.

- 1 'Application for a Parallel Import Licence': for applications for authorisation to import and distribute a product
- 2 'Application for Addition of a Source Country to a Parallel Import Licence': for applications to add further source countries after a parallel import licence has been granted
- 3 'Application for a Variation to a Parallel Import Licence': for applications to make changes to the parallel import licence other than additional source countries
- 4 'Application for Renewal of a Parallel Import Licence': for applications for renewal of a parallel import licence

There is a single form for application for a Dual Pack Import Registration. This is entitled: 'Application for Dual Pack Import Registration'.

Using the application forms

The application forms are designed as templates and can be used as such or used in hard-copy format. They are available in electronic form, please see the 'Publications and Forms' section of www.hpra.ie.

General guidance

- 1 Where an electronic SmPC is submitted on a CD-ROM, it should be sent on a PC-compatible CD, in a Word-compatible format.
- 2 Package leaflets in the imported product may be submitted as originals or as photocopies.
- 3 Columns marked 'for HPRA Use Only' should be left blank.

Comparative product details

In the application forms for a new parallel import licence, to add a source country and to renew an authorisation, details of the Irish and imported product are required to be submitted in a tabular format. The details for the Irish product should be taken from the label and leaflet of the product marketed in Ireland and the details for the imported product from the label and leaflet of the imported product. The details may also be available from the SmPC of the Irish and/or imported product, if these are publicly-available documents.

The line listing of excipients is used to determine whether or not it is reasonable to presume that the Irish and imported products are therapeutically equivalent. Therefore, it is important to present the list in a manner which facilitates this determination. Each excipient should be listed on a separate line. Where the same excipient is present in both the Irish and imported product, they should be listed on the same line in the relevant columns, as in the following examples:

Comparative Product Details	Ireland	Member State or EEA Country <i>Insert Name</i>
Line list of excipients	Lactose Magnesium stearate Microcrystalline cellulose	Lactose Magnesium stearate Microcrystalline

Where the same excipient is given a different name in the Irish patient information leaflet and in the imported product's leaflet, they should still be listed on the same line. This also applies where different salt or hydrate forms are used, as in the following example:

Comparative Product Details	Ireland	Member State or EEA Country <i>Insert Name</i>
Line list of excipients	Lactose Methylhydroxypropylcellulose Polyvidone Silicon dioxide	Lactose monohydrate Hypromellose Povidone Colloidal anhydrous silica

Where different excipients are present, they should be presented on different lines:

Comparative Product Details	Ireland	Member State or EEA Country <i>Insert Name</i>
Line list of excipients	Propylene glycol Cellulose acetate Hypromellose Polyethylene glycol - - -	- - Methylhydroxypropylcellulose - Crospovidone Maize starch Lactose

One table should be completed per source country.

APPENDIX 3 DOCUMENTATION REQUIREMENTS FOR VARIATIONS TO PARALLEL IMPORT LICENCES

The condition and documentation requirements associated with each defined category of variation are outlined in the 'Application for a Variation to a Parallel import Licence' form found on the HPRA website. The HPRA reserves the right to request additional documentation to the required documents as outlined in the application form, where deemed necessary. The following general rules apply in every instance:

- Each application for a variation to a parallel import licence should be made using the application form 'Application for a Variation to a Parallel Import Licence' available on the 'Publications and Forms' section of www.hpra.ie.
- A brief background explanation for the proposed change should be provided in every instance.
- The precise details of the proposed change should be stated in the present/proposed section of the application form.
- Where changes to the product information (SmPC/labels/leaflet) are proposed, these should be clearly highlighted by submitting present and proposed versions of each document.
- There is no requirement to submit documents in duplicate.
- Mock-ups of labels should be an accurate representation of how the product will appear on the market (i.e. all sides of the proposed packaging should be visible and all text, both existing and over-labelled, should be legible).
- Applicants are encouraged to submit applications in electronic format wherever possible.
- Where multiple changes are proposed, each change must be submitted under the appropriate variation category. Multiple variations may be grouped together on one application form provided each category is clearly stated.

APPENDIX 4 SmPC TEMPLATE FOR PARALLEL IMPORT LICENCES

1 NAME OF THE MEDICINAL PRODUCT

<(Invented) name, strength, pharmaceutical form>

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<Quantitative declaration of the active substance(s)>

<Excipient(s) with known effect: Insert details of such excipients>

<For the full list of excipients, see section 6.1.>

3 PHARMACEUTICAL FORM

<Pharmaceutical form>

Product imported from <name of source country>

<Visual description of product>

4 CLINICAL PARTICULARS

As per <include PA number of Irish product>

Where an excipient with a recognised action or effect is declared on the label, the relevant warning must be included in the SmPC, in section 4.3, 4.4 or 4.8 as appropriate. If the warning is not included in the SmPC for the Irish product it should be included in the SmPC for the PPA.

5 PHARMACOLOGICAL PROPERTIES

As per <include PA number of Irish product>

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<list of excipients as per the package leaflet of the product on the market in the source country>

6.2 Incompatibilities

<The appropriate statements should be included.>

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the packaging of the product on the market in the country of origin.

Details of the in-use shelf-life and in-use storage conditions may need to be included where applicable.

6.4 Special precautions for storage

<The proposed storage conditions should be based on the storage conditions of the Irish product and the source country product and where these are different the proposed storage conditions should be the more conservative of the two.>

6.5 Nature and contents of container

<Include a description of the container and pack size(s)>

<Not all pack sizes may be marketed.>

6.6 Special precautions for disposal <and other handling>

<Any special requirements for the handling and/or disposal of the product should be included here.>

7 PARALLEL PRODUCT AUTHORISATION HOLDER

<Name and address of PPA holder>

8 PARALLEL PRODUCT AUTHORISATION NUMBER

<PPA number>

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: *DD month YYYY*

<Date of latest renewal: DD month YYYY>

10 DATE OF REVISION OF THE TEXT

<Month YYYY>

**APPENDIX 5 SAMPLE FORMAT FOR NOTIFICATION TO MARKETING AUTHORISATION
HOLDER OF INTENTION TO PARALLEL IMPORT UNDER A DUAL PACK
IMPORT REGISTRATION**

Date

Contact person
Name of MA holder
MA holder address

Re: Notification of intention to parallel import **Product XXXX**

Dear Sir/Madam,

I wish to advise you that **DPR Applicant Name** intends to apply to the Health Products Regulatory Authority for a Dual Pack import Registration (DPR) to parallel import **Product Name (Size, strength and PA number)** into Ireland. The intended application date is one month from the date of this letter.

Yours faithfully,

DPR applicant contact name