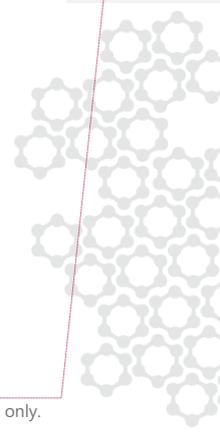


Guide to Labels and Leaflets of Human Medicines

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



CONTENTS

1	SCOPE	3
2	LEGAL BASIS	3
3	INTRODUCTION	4
4	PRESENTATION OF THE PRODUCT NAME ON THE LABEL	4
5	SPECIFIC LABEL REQUIREMENTS	5
6	SPECIFIC PACKAGE LEAFLET REQUIREMENTS	9
7	BRAILLE AND ACCESSIBLE PACKAGE LEAFLETS	10
8	CONSULTATION WITH TARGET PATIENT GROUPS FOR THE PACKAGE LEAFLET	15
9	ADDITIONAL INFORMATION ON THE LABEL AND IN THE PACKAGE LEAFLET	22
10	PROCEDURE FOR SUBMITTING AND APPROVING LABELS AND LEAFLETS	24
11	SAFETY FEATURES	28
ANNEX 1	EXAMPLE OF MULTILINGUAL LABELLING	30

1 SCOPE

The guidance in this document applies to the labels and package leaflets of medicinal products for human use, authorised nationally, through mutual-recognition or through the decentralised procedure. The guidance does not apply to medicinal products authorised through the centralised procedure.

2 LEGAL BASIS

The legal basis for the requirements relating to labels and package leaflets are in Directive 2001/83/EC on the *Community code relating to medicinal products for human use* as amended by Directive 2004/27 EC. The directives have been transposed into Irish law by the Medicinal Products (Control of Placing on the Market) Regulations 2007; these regulations apply to all applications submitted from 23 July 2007. For product authorisations granted or applications submitted before that date, the relevant regulations are the Medicinal Preparations (Labelling and Package Leaflet) Regulations 1993 (S.I. No. 71 of 1993) which gave effect to Council Directive 92/27/EEC (subsequently codified as 2001/83/EC). According to the transitional arrangements in the Medicinal Products (Control of Placing on the Market) Regulations 2007, the requirements of the Medicinal Preparations (Labelling and Package Leaflet) Regulations 1993 apply until 30 October 2010 to those product authorisations granted or applications submitted before 23 July 2007, after which time the requirements in the Medicinal Products (Control of Placing on the Market) Regulations 2007 will apply. The legal basis for the requirements relating to the safety feature appearing on the packaging of medicinal products is in regulation (EU) 2016/161.

For general guidance, the following EU guidelines are also applicable to labels and package leaflets:

- Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'
- Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use
- Note for guidance on Declaration of Storage Conditions A: in the Product Information of Medicinal Products B: for Active Substances
- Compilation of Quality review of documents decisions on stylistic matters in product information
- Guideline on Pharmaceutical Aspects of the Product Information for Human Vaccines
- Guideline on the Warning on Transmissible Agents in Summary of Product Characteristics (SmPCs) and Package Leaflets for Plasma-Derived Medicinal Products

3 INTRODUCTION

Product labels and the package leaflet play an essential part in the safe and effective use of the medicine by both the patients and healthcare professionals. Thus, the approval of the label and package leaflet is an intrinsic part of the authorisation process for all medicinal products.

The detailed requirements for the information to be included in labels and leaflets are specified in Articles 54–69 of Directive 2001/83/EC. Article 8(3) of the directive also requires that the application shall be accompanied ‘...by a mock-up of the outer packaging and of the immediate packaging of the medicinal product together with a package leaflet’.

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The EU guideline on the *Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use* provides a definition of a mock-up as ‘A flat art-work design in full colour, presented so that, (following cutting and folding where necessary), it provides a replica of both the outer and immediate packaging and of the leaflet and clearly demonstrates the three dimensional presentation of the label text and of the leaflet text’. The guideline also provides guidance on how best to present the printed label, e.g. font size, use of colours, lay-out, particulars for small immediate packaging, etc.

Labels and leaflets should be prepared in line with directive requirements and with the advice available in EU guidelines. Further additional advice is provided in this guidance document.

4 PRESENTATION OF THE PRODUCT NAME ON THE LABEL

The label must contain all elements required by Article 54 of Directive 2001/83/EC. For prescription medicines the invented name, the strength and the pharmaceutical form followed by the common name of the active(s) relevant to the strength in the name should appear in that order, as a cohesive unit and should not be separated by any interpolated text. Where there are multiple active ingredients, the strength of each active ingredient is to be included in the name.

However, for OTC and general sale products containing two or more actives the following OTC format may be used:

- *‘Invented name, pharmaceutical form*
- *INN 1, strength*
- *INN 2, strength*
- *INN 3, strength’*

Please note that where a company chooses this option for an OTC or general sale product, the entire text in italics above will be considered to be the product name. This product name must be listed as an integrated unit in section 1 of the SmPC, on all labels and leaflets and on all advertising related to that product.

5.3 Multilingual packaging

Directive 2001/83/EC, Article 63(1) permits the use of multilingual text with the proviso that the same information appears in all the languages used. The exception to this is text captured within the blue box. In this guide multilingual packaging refers to a package which is designed for two or more European languages.

Where medicine availability on the Irish market may be compromised with single-country packaging the HPRA actively encourages the use of multilingual labelling and package leaflet. The HPRA works closely with MAHs and other European regulators to help facilitate this and follows the principles of the CMDh Best Practice Guide on Multilingual Packaging.

The readability of the multilingual packaging must not be compromised when two or more languages are added to the package.

The HPRA will accept, by way of a 'blue box', countries' national requirements as highlighted in the Notice to Applicant's 'Guideline on the packaging information of medicinal products for human use authorised by the Union' and in the CMD(h) guidance on 'blue box' requirements, CMDh/258/2012. The minimum requirements in the 'Guideline on the readability of the labelling and package leaflet of medicinal products for human use', ENTR/F/2/SF/jr should also be followed.

Additional guidance can also be obtained in the EMA 'Compilation of QRD decisions on stylistic matters in product information', EMA/25090/2002.

A multilingual package must fulfil the following criteria:

- The name and the strength of the medicinal product is the same in all languages.
- The information in the SmPC is consistent with the information that appears on the labelling and the package leaflet.
- The information is clearly presented on the labelling and package leaflet so that it can be understood by those who see it and patients can use their medicines safely and appropriately.
- The legal status must be the same in both countries.

The HPRA will be flexible specifically in relation to the following:

- **mL in IE vs ml in other EU states:** We can permit the use of ml or mL.
- **Decimal point in product strength or volume - dot in IE vs comma in EU:** This can be overcome by repeating the invented name, the strength and pharmaceutical form as a cohesive unit in each language or by grouping information relating to the strength and pharmaceutical form, in the different languages, immediately next to the invented name.
- **Thousand separator in product strength or volume - comma in IE vs dot in EU:** This can be overcome by repeating the invented name, the strength and pharmaceutical form as a cohesive unit in English using the comma or a space as the thousand separator, or by expressing the composition on the side panel of the outer carton.

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Note: The use of commas instead of dots can be accepted on multilingual immediate and outer packaging labels where absolutely necessary due to space constraints, where no risk of confusion exists and where the medicine is considered critical to the Irish market. Otherwise the above requirements apply. For centrally authorised products, prior agreement with the HPRA should be sought and the agreement email can be provided to the EMA.

- **Small immediate packaging units:** Small immediate packaging units are defined as containers sized up to and including 10 ml where only minimum particulars are required. On a case-by-case basis the minimum particulars could also be considered for other containers where it is not feasible to include all the information. As such, for multilingual labels where there are space constraints, the HPRA can accept minimum particulars on containers up to and including 50 ml where justified, particularly for more than two languages. Where product information is harmonised between member states (e.g. via a mutual recognition procedure), applicants should ensure that minimum particulars are specified in the common texts for containers of the required size, referencing the need for reduced space for multilingual labelling for IE and other member states.
- **Use of one language:** In some cases, multilingual packaging in the EU have made use of one language for certain particulars in order to save space, e.g. English or Latin are commonly proposed for particulars such as INNs. The HPRA can accept English as a common language without further justification. The use of Latin will be considered where absolutely necessary due to space constraints, where no risk of confusion exists and where the medicine is considered critical to the Irish market.
- **Third country information:** Multi-country packs with the UK are acceptable on the condition that the product information is the same in the UK and IE and that additional UK administrative information is placed in the 'blue box'. Examples of administrative information include the name and address of the MAH, the MA number and the UK site of batch release. **Note:** MAH and MA number information from other EU member states is acceptable. It is acceptable to add, change or delete these details without prior notification to the HPRA, see section 10.3.
- **Coordinating assessment with other member states:** As multiple member states are likely to be involved in the assessment of the mock-ups, the HPRA can be flexible on other aspects where justification is provided. Applicants can facilitate this by coordinating and sharing comments from different member states (MS). The HPRA can assist with aligning our approval times with any other MS as required once this information is imparted to us by the applicant. We can also assist in directly liaising with the other MS(s) if the other MS(s) is/are also agreeable to this.
Note: The HPRA can work as part of the Nordic procedure if required.
- **Joint names:** Applicants should highlight to the HPRA when proposing an invented name, if it has been proposed to other MS, with which multilingual packaging are being developed.

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Additional recommendations to be taken into consideration:

- Information in English should be blocked together where possible.
- Where a number of countries share a common pack, list the 'blue box' requirements for all countries on the same panel/side.

- Country-specific requirements, such as 'blue box' text, must specify the country to which this applies, e.g. 'IE' or 'Ireland' before the text.
- For the package leaflet: a clear indication that the text following applies to Irish patients, e.g. a two letter language code in an oval before the English language text: **EN**
- It is acceptable for perforated sections to be present on the pack, provided that the removable information is not the English language section. This should be indicated in the submission.
- A pdf of the Ireland only package leaflet must be supplied to the HPRA at the end of the procedure so that it can be uploaded to the HPRA website.

For further assistance, an example of multilingual labelling is displayed in Annex 1 below. Note this is an example of trilingual labelling where it may not be possible to keep English language text together. It is acknowledged that this is only an example and that other layouts are acceptable.

For further advice on the design of multilingual labelling, including those authorised via the centralised procedure where prior discussion with the HPRA may be necessary, please contact the HPRA's Customer Services section at info@hpra.ie.

5.4 Labels of vaccine products and plasma-derived medicinal products

The labels of vaccine/plasma-derived medicinal products should contain peel-off label(s) on the immediate packaging to allow a record of critical information to be retained. This facilitates the traceability of administered doses of vaccines/plasma-derived products and the recording of batch numbers and expiry dates.

The peel-off label(s) should contain, at minimum, the following information:

- Invented name of the vaccine/plasma-derived medicinal product
- Batch number
- Expiry date

The overall readability of the statutory information displayed on the fixed part of the label should not be affected by the inclusion of the peel-off part. The information provided in the peel-off label should always remain available on the fixed part of the label once the peel-off part is detached.

Any exceptions to these requirements should be discussed in advance with the HPRA and will be considered on a case-by-case basis.

5.5 Label/leaflet combinations

Label/leaflet combinations present greater challenges in ensuring that the information is presented in a legible manner. For the package leaflet, a type size of at least 9 points as measured in font Times New Roman, not narrowed, with a space between lines of at least 3 mm, is considered as a minimum. However, for marketing authorisation applications until 1 February

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2011, a type size of 8 points may be accepted on a case-by-case basis assuming legibility is not compromised. The particulars appearing on the label should be printed in characters of at least 7 points leaving a space between lines of at least 3 mm.

The outermost face of the leaflet and the leaflet face in closest contact with the packaging (at the end of the leaflet) are both considered to be the immediate packaging label and the information that appears on each of these must be identical and meet all requirements of Directive 2001/83/EC for labelling and medicinal products.

The point of opening of the leaflet should be clearly identifiable to the user by helpful phrases such as 'open here' (or similar). It should be possible to open and reseal the label/leaflet combination. For further guidance on the presentation of label/leaflet combinations (fix-a-form labels), please refer to the [IMB Newsletter Issue Number 33](#) available in the Newsletters & Reports section on the HPRA website.

5.6 Declaration of strength for liquid parenterals

The quantity per millilitre (ml) and the total amount per total volume should be listed on both the inner and outer label.

5.7 Labelling of peel-off blisters

Peel-off blisters are often required for oro-dispersible tablets due to their fragility. For this reason, the HPRA recommends that clear information on how to remove the tablets from the blisters should be included in the SmPC, package leaflets and labels. Suggested approaches are as follows:

- If space permits on the outer carton, a statement referring the user to the package leaflet for instructions on how to remove the tablets should be included. For example, 'See package leaflet for details on how to open the blister'.
- For blister labels, it is recommended that a pictogram indicating that the tablets should not be pushed through the blister is included on one side of the blister. On the other side, it is recommended that a distinctive arrow, indicating the point where the blister is to be peeled from, should be included.

For further guidance on the labelling of peel-off blisters, refer to the [IMB Newsletter Issue Number 35](#) available in the Newsletters & Reports section on the HPRA website.

6 SPECIFIC PACKAGE LEAFLET REQUIREMENTS

6.1 Compliance of the package leaflet with the SmPC

In drawing up the leaflet, the name that appears at the top of the leaflet must correspond completely with section 1 of the SmPC, i.e. name, strength and full pharmaceutical form

followed by the INN. Applicants should note that all of the information contained in the SmPC should be included; this applies especially to precautions, warnings and all listed undesirable effects.

6.2 Technical package leaflets

Technical package leaflets are not required for all products but are recommended (according to the QRD template) in the following instances:

- Practical information and/or administration of the medicinal product by the patient needs to be provided when such information is too extensive to be included in section 3 (How to take/use X) of the package leaflet. A cross reference should be included in section 3.
- For parenteral products or other products which are mainly used in hospitals, practical information on preparation and/or handling of the product can be included for healthcare professionals, where relevant and a cross reference to section 3 should be included.

If other information is to be included in the package leaflet for the healthcare professional, the applicant should provide the complete SmPC or appropriate sections of the SmPC as a tear off section at the end of the package leaflet, so that the information for the patient (the package leaflet) and the information for the healthcare professional (the SmPC) are clearly differentiated. The information for the healthcare professional should correspond fully with the SmPC.

7 BRAILLE AND ACCESSIBLE PACKAGE LEAFLETS

7.1 Introduction

In order to ensure improved access to information on their medicines for people with visual impairment, Article 56a has been introduced under Title V of Directive 2001/83/EC as amended by Directive 2004/27/EC. These requirements are implemented by S.I. 540 of 2007 Medicinal Products (Control of Placing on the Market) Regulations 2007. This requires that the name of the medicinal product must be expressed in Braille format on the packaging, allowing improved differentiation of medicines. It also requires that the marketing authorisation holder ensures that the package leaflet is available on request in formats which are suitable for people with visual impairment. The 'leaflet' provided should not be abridged in any way.

7.2 HPRA requirements

The following approach is being taken by the HPRA to ensure compliance with this requirement.

A 'Braille Declaration Form', available on the 'Publications and Forms' section of www.hpra.ie, must be provided by the applicant for all new applications, at renewal and for variations to update patient information in line with the provisions of Article 56a. Braille declarations are not required initially where a product is not to be marketed and text versions of national labels and leaflets have been submitted, e.g. at the end of a DCP procedure. The Braille declaration must

then be submitted during the Article 61(3) notification to register the mock-ups prior to marketing.

The relevant sections 1a or 1b, and 2 must be completed and the declaration must be signed and dated by the applicant's authorised representative. HPRA assessors will assess that the wording to be provided in Braille is in line with the requirements of the EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use.

Applicants must include in Braille the invented name, strength (where the product is available in more than one), and the pharmaceutical form (where a risk of confusion occurs), on the outer carton of medicinal products. Products which are for administration by healthcare professionals only are excluded.

Applicants should note that even where section 1b of the declaration has been completed (stating that no Braille is required as the product is for administration by healthcare professionals only), section 2 must nonetheless be completed, as package leaflets for all medicines must be available in formats suitable for blind or partially-sighted people. For existing product authorisations, where applicants wish to delay implementation of one or other section, i.e. either Braille or accessible leaflets, in line with the transitional arrangements in Part 5 of the Medicinal Products (Control of Placing on the Market) Regulations 2007, the declaration should be annotated to this effect.

The Market Compliance Section of the HPRA Compliance Department checks compliance with the labelling and other provisions of Article 56a. As part of this work, the Market Compliance Section obtains samples of relevant medicinal products from the marketplace for checking, and also performs inspections, as necessary, in order to monitor compliance with the provisions of Article 56a and with the declaration provided.

The requirement to comply with Article 56a applies to MRP/DCP products authorised after 30 October 2005 and is applicable to all new applications for product authorisations submitted nationally since 23 July 2007. Therefore, all authorisations must be in compliance with labelling and leaflet requirements under Title V of the directive. Applicants must meet the requirement to provide the leaflet in a format suitable for people who are blind or partially sighted ('patient accessible' leaflet).

Grade 1 Braille, which is uncontracted Braille, is the required type of Braille for use on medicinal packaging in Ireland.

Note that, since March 2017, Unified English Braille (UEB) has been the preferred type of contracted Braille for use in Ireland generally, and that previously Standard English Braille (SEB), another type of contracted Braille, had been in use. The change to UEB from SEB should have no impact on most of the Braille applied to medicines packaging, with the exception of the Braille used for some mathematical symbols. Applicants should satisfy themselves that the Braille used

for any mathematical symbols on its product packaging is in a format suitable for patients in Ireland, is easily readable and clearly comprehensible.

To date several issues have arisen which have necessitated clarification and these are highlighted below.

- The timelines for implementation of these variations follow current implementation timelines.
- The format of Braille to be used should be in line with the requirements of the European Braille guidance now incorporated in the EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use.
- The Braille declaration form submitted must show exactly what information appears on the carton including units, backslashes, etc. Where applicable, a space should be present between the strength and units of the product (i.e. 50 mg instead of 50mg). This space is important for Braille readers as the same Braille dots (up to the letter J) are used for both letters and numbers, and this space indicates that the Braille dots have changed from numbers to letters.
- There is no requirement for flat dot mock-ups to be provided at this time. Normal mock-ups should be provided along with the Braille declaration to indicate from which label version onwards the Braille declaration applies.
- Generally, one Braille declaration form should be provided per PA and will be kept on file (although multiple strengths of the same product form, e.g. tablets, could all be listed separately on the same declaration). For example, the Braille declaration form should be updated if there is a change in product name, if for PA5555/222/1, PA5555/222/2 and PA5555/222/3 the following text appears on the Braille declaration form:
 - o 'Invented name x mg
 - o Invented name y mg
 - o Invented name z mg'
- If there is a change in packaging layout, e.g. an Article 61(3) notification, applicants must satisfy themselves that this does not affect the legibility of any text now underlying the Braille (e.g. indications, posology, strength), to maintain compliance with the Braille declaration on file.
- The Market Compliance Section of the HPRA's Compliance Department checks that the information provided in Braille on the carton is that which was stated in the Braille declaration on file and correctly interpretable.
- Where a product is for administration by the patient themselves, Braille must appear as per the recommendations of the EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use.

- The quality of the embossing mechanism and medium used must be carefully evaluated to ensure that the carton will still be readable at the end of shelf life. In particular, the height of the Braille dots is important to facilitate the readability of the Braille. Low dot height has frequently been an issue when compliance checks have been performed on Braille by the HPRA. Applicants are advised to consider I.S. EN ISO 17351:2014 'Packaging – Braille on Packaging for Medicinal Products' when ensuring that the Braille dots are of a sufficient height to enable one to read the Braille correctly. This standard sets out the Braille dot height criteria as follows:

- o The dot height target for the Braille cell should be 0.20 mm.
- o Not more than 5% of the Braille cell dot height measurements should be lower than 0.12 mm.
- o Not more than 1% of the Braille cell dot height measurements should be lower than 0.10 mm.

The key goal of this standard is to ensure sufficient Braille dot height is achieved in order to ensure the readability of the Braille. In this regard, a minimal Braille dot height of 0.12 mm is generally regarded as acceptable by the HPRA. Compliance with this ISO standard is not currently a GMP requirement. The GMP guide does not directly address Braille tests or checks at this time, and the HPRA recommends that medicinal product manufacturers consider this ISO standard as it can facilitate compliance with the legally binding company (MAH) Braille declaration for each product which commits to Braille text that is easily readable.

- Braille may be extended over more than one face of a carton, or oriented differently to the printed text. However, if this approach is taken it is the applicant's responsibility to ensure that the readability of the Braille text is not compromised.
- Hyphenation of long words in Braille may be carried out in line with the general rules for everyday Braille. It is the applicant's responsibility to ensure the Braille is clearly comprehensible and in a format suitable for Irish patients.
- The EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use allows for contracted (Grade 2) Braille to be used for small containers with a capacity of less than 10 ml and also suggests that innovative packaging, e.g. tab label, should be used where space issues arise. To date the HPRA has accepted a justification for using the contraction 'o*t;t' for an ointment in a pack size less than 10 ml. The Braille declaration in such instances should include in English text an exact reflection of what appears in Braille on the carton and its explanation (ointment) for future reference.
- Braille may be included by the applicant on cartons or bottles via a permanent overlabel if necessary, providing the requirements of the Braille declaration are still fulfilled and no text on the cartons or bottles is obscured by the overlabel.

- It may be acceptable not to include Braille on bulk dispensing packs, where the applicant submits a justification that certain pack sizes are 'for administration by healthcare professionals only' as per the EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use. The Braille declaration must be annotated to state to which pack sizes Braille is applied, and in all cases section 2 must be filled out.
- Where the invented name of their product in Braille (accompanied by the strength and form if necessary) is too long to be displayed effectively in Braille on the carton, applicants should consider a variation to register a shorter invented name, as the invented name in Braille must match the invented name registered in section 1 of the SmPC and on the patient leaflet, to avoid confusion and as per EU guidance.
- Braille declarations must also be submitted for existing products where Braille may have been historically included but never assessed for compliance with the current EU requirements.
- It is not considered necessary for PPA holders to overlabel Braille on cartons from other markets where they have checked and verified the following:
 - o that the Braille shown matches the requirements for the Irish market with regard to inclusion of the Irish invented name and strength and/or form where required,
 - o that the Braille is in a format suitable for Irish patients, is still easily readable, clearly comprehensible and does not interfere with the legibility of the underlying text or cause confusion for the patient, and they have signed and submitted a Braille declaration to that effect.
- Addition in Braille of an abbreviated pharmaceutical form, e.g. 'tablet' where the full pharmaceutical form is 'prolonged release tablet' should be avoided even if the preparation is only available in one form. Either the form should be omitted as per EU guideline or the full form added, to avoid any assumption that the product is immediate release.
- Further guidance has previously been published in IMB Newsletters:
 - o [Newsletter No. 31](#) September-December 2008 (re previous deferrals of requirements);
 - o [Newsletter No. 27](#) May-August 2007 (re submission of Braille declaration to cover patient accessible leaflets);
 - o [Newsletter No. 26](#) January-April 2007 (re Braille alphabets, market compliance activities, pharmaceutical form, dot heights);
 - o [Newsletter No. 22](#) September-December 2005 (re findings from market surveillance);
 - o [Newsletter No. 21](#) July-September 2005 (new legislation).

7.3 'Accessible' leaflets

MA holders are required by Article 56a of Directive 2001/83/EC to provide patient information leaflets in formats suitable for blind or partially sighted people. Such formats could include Braille, audiotape, CD or large print. Choice of the appropriate medium should be made by the

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MAH in consultation with representatives of organisations for the blind and partially sighted. For new applications, renewals or variations to update in line with the provisions of Directive 2001/83/EC, a Braille declaration form to confirm compliance with the requirements of Article 56a must be supplied as described in 7.2 above.

These 'accessible' leaflets will not be assessed by the HPRA but must contain the same information in the order of the directive as the approved leaflet and must not be abridged in any way. The Market Compliance Section of the HPRA Compliance Department checks availability of suitable 'leaflets' and that the current version is being supplied.

The requirement for 'accessible' leaflets, i.e. leaflets to be available in formats suitable for people with visual impairment applies for all PAs.

The following should be noted:

- Applicants should ensure the 'patient accessible' leaflet is available promptly to the patient on request, especially considering situations where medicine is used for short-term illness, and ensure that the format used is such that the patient can consult the leaflet again at their convenience.
- Where no separate patient leaflet exists as the information required has been provided on the outer carton, the applicant must provide this information in a format suitable for blind or partially sighted patients, and submit a Braille declaration accordingly.
- The HPRA does not endorse any particular service provider for the production of patient accessible leaflets and Braille implementation. It is the responsibility of the applicant as per the Braille declaration they have signed, to ensure the Braille and patient accessible leaflet are suitable for Irish patients.
- PPA holders must also comply with the requirement to promptly provide the leaflet in a format suitable for blind or partially sighted people on request, and this must be suitable for patients in Ireland.

8 CONSULTATION WITH TARGET PATIENT GROUPS FOR THE PACKAGE LEAFLET

The purpose of this section of the guidance is to assist applicants in ensuring that the final package leaflet (PL) reflects the results of testing with patients so that it meets their needs and enables the patient to use the medicinal product safely and effectively. The guidance will apply to applications for new marketing authorisations (MAs), significant variations to MAs, renewal applications, and applications where harmonisation of the PL is undertaken and which must be accompanied by data demonstrating compliance with Article 59(3) of Directive 2001/83/EC.

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8.1 Background and legal basis

The legal basis for the submission and approval of user testing of package leaflets is detailed in Article 59(3) and Article 61(1) of Title V of Directive 2001/83/EC and S.I. No. 540 of 2007, Medicinal Products (Control of Placing on the Market) Regulations 2007.

Articles 59(3) and 61(1) of Directive 2001/83/EC require that the package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use and that the results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority.

Results of such a readability test or justification for not providing it should be submitted in Module 1.3.4.

8.2 Circumstances where user testing is required

Submission of user testing of leaflets is required for all new applications and existing authorisations as follows:

National, mutual recognition, decentralised and centralised procedures:

- New applications submitted on or after 23 July 2007 (which is the date of transposition into Irish law of S.I. 540 of 2007) including line extensions if the original product in the series has not undergone user testing
- New products and new chemical entities
- Variations for change in legal status
- Inclusion of a novel presentation
- Addition of new indications with critical administration issues
- Medicines with critical safety issues
- New safety issues
- New leaflet format or layout

Changes to the format and layout which require user testing include:

- Change in font style used
- Change in typographical emphasis
- Change of colours used
- Change in style of writing and language used
- Addition/removal of pictograms
- Change in layout of critical safety sections of the package leaflet
- Switch to a fix-a-form leaflet

User test outcome reports should be submitted as Type IB variation procedures under category C.I.z. This includes situations where the results of user consultation may indicate that no changes or only minor changes are required to the product information. Implementation of the approved leaflet and packaging will be six months after the variation approval date.

Changes to the format and layout which do not require user testing include:

- Change in font size (once not below minimum of 9 point)
- Change in package leaflet dimensions
- Change in orientation of the leaflet (text)
- Change in the number of columns/pages in the leaflet

In cases where user testing is not required, an Article 61(3) notification should be submitted for the amended leaflet mock-ups.

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8.3 Exemptions from user testing

The evidence from tests on similar package leaflets may be used where appropriate and accompanied by a bridging report identifying and justifying any differences. Bridging reports should be submitted as Type IB variations under category C.I.z.

Examples of when this may be considered acceptable based on a sound justification by the applicant/marketing authorisation holder are:

- Reference to the PAR or EPAR of an identical package leaflet which has already been the subject of user testing (see CMD(h) Q & A Product information/Information on Medicinal Products), which also provides details of the documents which are required to be submitted, in order to qualify for this exemption.
- Line extensions. Bridging will generally be acceptable for package leaflets of the same active substance but with different strengths or routes of administration.
- Products which are not marketed in Ireland. If it is intended to market a product, then a user test must be performed, submitted and approved before the product can be placed on the market.

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The expectation with respect to the holders of parallel import licences is to maintain the parallel import licence and in this case, product information, in line with the PA product.

8.4 Methods by which MAHs can meet the requirements

The options available to MAHs of licensed, marketed products in Ireland for meeting the user test requirements are:

- 1 To submit a stand-alone user test report on a package leaflet.
- 2 To submit a bridging report to another package leaflet(s) user tested and approved by another Member State, i.e. a package leaflet that has been user tested and approved by the MHRA (see below).
- 3 Exemption from user testing (accompanied by appropriate justification).

A user test report of a package leaflet (termed 'parent' leaflet) can be used to fulfil the requirements of another leaflet (termed 'daughter' leaflet) if certain criteria are fulfilled. A bridging report comparing, contrasting and justifying the use of the parent user test report in

support of the daughter leaflet must also be provided. In addition, the need for focus user testing should be discussed.

In some circumstances, it may be appropriate for some daughter package leaflets to rely on the results of testing for more than one parent package leaflet, i.e. a double bridge. For example, it would be possible to refer to the design and layout of one leaflet and to the content of the leaflet for another product.

The number of permissible bridging relationships should be limited to two or three.

Criteria for acceptable bridging

One or more of the following to be used as justification for bridging:

Medicines in the same drug class

Bridging will normally be acceptable for package leaflets for medicines in the same therapeutic class where the clinical information set out in the SmPC (and therefore the information in the PL) is similar.

Importantly the key messages for safe use with the related medicines should be similar. However, the format and layout of the package leaflets to be bridged should be identical. This means that the daughter package leaflet should be revised and drawn up in a design, layout and linguistic style which conforms to the parent package leaflet which will have been the subject of a successful user test.

A therapeutically similar product is defined as a group of medicines which have similar modes of action. The following examples are included but this list is not exhaustive.

Cardiovascular	Thiazide and related diuretics
	Beta-blockers
	ACE-inhibitors
CNS	SSRIs
	Tricyclic and similar antidepressants
	Antihistamines
	Benzodiazepines
	Opioid analgesics
Anti-infectives	Penicillins, cephalosporins and macrolides
	Antifungals
Musculoskeletal	NSAIDs
Endocrine	Glucocorticoids
Malignant disease	Alkylating cytotoxics
Nutrition	Intravenous nutrition
Obstetrics/Gynaecology	Oral contraceptives

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Line extensions

Bridging will normally be acceptable for package leaflets of the same active moiety for different strengths or routes of administration. In these cases, the parent package leaflet should be the one which contains the more/most complex information for the patient. Where potentially similar products require the patient to understand significantly different methods of administration, different criteria will apply. Examples include but are not restricted to an inhalation device and a patch, where it will be important to ensure that the information in relation to the posology has been the subject of a successful user test. However, a daughter package leaflet could rely on user tests carried out on the package leaflets associated with more than one product. For example, a double bridge could be applied to the package leaflet for a salbutamol inhaler (daughter) which could be bridged to a successful user test for a package leaflet for an oral salbutamol preparation (covers information relating to the active moiety) and to the package leaflet for a beclometasone product with an identical inhaler device (covers information relating to delivery).

Same key messages for safe use

Where the key messages for safe use which have been identified for a range of medicines are similar and the package leaflets are designed, laid out and written in an identical manner, bridging here will be easiest to justify.

Combination medicines

Generally, the package leaflet for the combination medicine should be considered as the parent package leaflet for the purpose of bridging to the individual component daughter package leaflets. It will be necessary to make sure that any key messages for safe use relating to the individual components have been addressed in the questionnaire for the combination package leaflet. It may be possible to use the individual component package leaflets as the parent package leaflets and bridge to the combination package leaflet as the daughter, provided any differences in layout and length of the combination package leaflet have been the subject of successful user testing within the company portfolio.

Short PLs for medicines with minor therapeutic actions and very low risk profile

Short PLs for such products are unlikely to need to be the subject of a specific user consultation. It will be sufficient to rely on the successful consultations carried out for other products within the portfolio even though these may not be in the same therapeutic class. Examples of such medicines are water for injection, aqueous cream, hypromellose eye drops.

Pictograms

Pictograms used within a company house style will need to be tested as part of a user test. For bridging to encompass pictograms successfully the pictograms in daughter package leaflets should have the same design, dimensions and colours as those in the parent package leaflet.

8.5 Submission requirements

Applicants should present the results of user testing in English in a standardised 'User Test Outcome Report', including at least the following information, in Module 1.3.4 of the application:

Stand-alone report:

- 1 Cover letter
- 2 Application form
- 3 User test report to include (but not limited to):
 - Introduction/product description
 - Test details, such as:
 - o Method used, test protocol
 - o Explanation on the choice of test population
 - o Language(s) tested
 - Questionnaire (including instructions and observation forms)
 - The original and revised package leaflets
 - Summary and discussion of results (i.e. subjects' answers, model answers, problems identified and revisions made to relevant package leaflet section)
 - Conclusion

Bridged report:

- 1 Cover letter
- 2 Application form
- 3 Bridged report to include (but not limited to):
 - Introduction/product description
 - Justification for bridging
 - Bridging procedure
 - Comparison of package leaflet with bridging package leaflet(s) – see Table 1
 - Package leaflet user testing methodology
 - Summary of test results
 - Discussion of results
 - Any other relevant information
 - Conclusions
 - Focus user testing as appropriate

Table 1:

A tabulated illustration of the comparison/contrast and justification of the parent package leaflet to the daughter package leaflet would be beneficial. An example is provided:

Package leaflet section	Parent package leaflet text	Daughter package leaflet text	Summary of differences	Comment on the effect on readability

8.6 The format of the assessment

8.6.1 Design and layout

The presentation of the information in the package leaflet is crucial to the way in which patients access the key messages for safe use. The following important aspects should be considered in both 'stand-alone' user test reports and bridged user test reports:

- Font and font size
- Headings and sub-headings including consistency of placement
- Package leaflet dimensions including whether the document is laid out in portrait or landscape format
- Use of colour and choice of colour
- Style of writing and language used
- Layout of critical safety sections of the package leaflet
- Use of pictograms

The QRD template should be followed as much as possible. In exceptional cases, alternative headings may be acceptable, especially for those headings containing <take><use> or where a different wording would be more appropriate for the product concerned, e.g. to better reflect the user of the product. This should not in any case impact on the content required for the section concerned. Applicants should justify the use of alternative headings referencing user testing results.

In order for bridging to be successful both the parent and daughter package leaflets should have a common design, layout and style of writing.

8.6.2 Technical aspects

MAHs should ensure that the user test meets the following criteria:

- The most important information must be clearly defined, for example, what the medicine is for, the dosage and any significant side effects and warnings.

- The test sample populations who are particularly likely to rely on the leaflet for the medicine in question (these may include carers) must be reflected in the report.
- A clear protocol for the user test must be presented.
- Evidence that test participants can find and appropriately use the information must be provided.

Where it is intended to market a medicine in Ireland, any user testing undertaken should be on the English language version of the patient information leaflet.

8.6.3 Key issues to be addressed in a successful bridging report

- Identifying key messages for safe use (of both parent and daughter package leaflet – the differences should be addressed and/or risk assessed):
 - o The key messages for safe use within daughter package leaflet should be discussed.
 - o How these are covered within the test carried out on the parent package leaflet should be justified.
 - o Where key messages are not identical, the bridging report will need to critically appraise these differences and address their relevance to the daughter package leaflet.
 - o Synergies and similarities in the key messages should be discussed.
- Design and layout issues:
 - o A critical comparison of the design and layout of both daughter and parent package leaflets should be presented.
- Complexity of message and language used:
 - o A critical discussion of the complexity of the messages contained within the parent and daughter package leaflets should be presented.
 - o The language used in both package leaflets should be discussed and compared.
 - o Differences and similarities should be discussed.

9 ADDITIONAL INFORMATION ON THE LABEL AND IN THE PACKAGE LEAFLET

Article 62 in Directive 2001/83/EC, states that the outer packaging or package leaflet may include ‘...symbols or pictograms designed to clarify certain information mentioned in Articles 54 or 59(1) or other information compatible with the SmPC which is useful for the patient, to the exclusion of any element of a promotional nature’. Therefore, symbols, pictograms or pictures or other text may only appear on outer labelling as long as they are in line with the SmPC, are not promotional nor misleading, and do not interfere with legibility. Guidance on the acceptability of certain additional information is given below.

9.1 General information on the medical condition

Information on the condition for which the product has been prescribed may be included in the leaflet, provided it is in line with the requirements of Article 62 of Directive 2001/83/EC.

9.2 Websites

Website addresses are not permitted on the label or leaflet, whether they are sites related to the PA holder or to the particular product. References to websites, coupons, product-specific phone lines, mail clubs, etc., are considered to be promotional in nature and are not permitted. References to other websites, such as those for patient organisations or for medical conditions are not acceptable. The only exception to this is when including the URL of the platform hosting the content of an approved mobile technology feature (refer to EMA/493897/2015 and CMDh/313/2014 for further information).

9.3 Telephone numbers and email addresses

Telephone, fax numbers or email addresses for the PA holder are acceptable on the label and/or leaflet as long as they are accessible to Irish patients. They can also be included in the printed version of the SmPC used by the PA holder but will not be included in the SmPC which is part of the PA schedule. Emails linking to websites are not acceptable - see above.

9.4 Accreditation logos

Accreditation logos or statements, e.g. for 'organic', 'Kosher', 'Halal', 'Guaranteed Irish' are not acceptable on the label or leaflet, with the sole exception of the recycling symbol which may be used on the label or leaflet in line with EU requirements for recovery and recycling of packaging waste under Directive 94/62/EC.

9.5 Patient registration forms

Forms in the package leaflet or coupons which request patients to send their details to the PA holder for further information are considered promotional and not acceptable.

9.6 Patient organisation details

Contact details for independent patient organisations may be included in package leaflets, e.g. phone or fax numbers (as long as they are accessible to Irish patients), email addresses, but not websites (as above).

9.7 Quick response (QR) codes or 2D barcodes on labelling and in package leaflets

The addition of a QR code or 2D barcode to product labelling or package leaflets is permissible provided all three of the following conditions are met:

- 1 The QR code or 2D barcode is intended for internal manufacturing processing, stock control or anti-counterfeit measures.
- 2 Any additional information in the QR code or 2D barcode which can be read by members of the public must not contain information other than product information approved by the HPRA for inclusion in the SmPC, label or package leaflet for that product.
- 3 The addition of the QR code or 2D barcode does not affect any other aspect of the label or leaflet and does not affect the legibility of the approved label or leaflet text.

Addition of QR codes or 2D barcodes fulfilling all three of the above requirements will not require submission of a variation application. However, where the addition of such a code or barcode meets conditions 1 and 2 but does not meet condition 3, an Article 61(3) notification should be submitted along with amended mock-ups for consideration.

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It will be the responsibility of the MAH to ensure that all three of the above conditions are met.

The general principles and procedural rules for mobile scanning and other technologies in the labelling and package leaflet of centrally authorised medicinal products has been published by the EMA (EMA/493897/2015). For other procedures, please see CMDh/313/2014. Addition of and changes to these technologies (with the exception of cases covered by the three above conditions) will require a variation application.

9.8 Use of 'New' on packaging or package leaflet

Statements such as 'New' or 'New product' may not be used for promotional purposes on product labelling.

'New' may be used on product labelling in order to alert pharmacists and patients to a change in an existing product of which they should be aware or which might give rise to concern in the absence of such comment (changes in the composition, appearance, colour, shape, flavour, markings, etc.). In these cases, 'new' must qualify the property which has changed, e.g. 'New markings', 'New formulation'. This statement should be included for a period of six months only.

10 PROCEDURE FOR SUBMITTING AND APPROVING LABELS AND LEAFLETS

10.1 New and renewal applications

10.1.1 Submitting labels

All new and renewal applications, either national or MR/DCP must include colour mock-ups of the labels if the product is marketed (text-only versions are acceptable if the product is not marketed), in order to facilitate an accurate review of compliance with directive and guideline requirements. A 'text-only' version of the label is the provision of the text that appears on the label using the QRD/CMDh template headings. Label mock-ups may be submitted either

electronically as scanned versions of mock-ups (one copy of each mock-up), or as a pdf document (one copy of each mock-up). Hand-amended mock-ups may be accepted during the assessment phase of an application but the final label mock-ups (whether colour mock-ups or text-only versions) must have all the required information incorporated into the printed text. Applications with text-only labels will only be accepted if the product in question will not or has not been marketed in Ireland. The applicant must submit full colour mock-ups of the labels by way of Article 61(3) notification to the HPRA for approval prior to marketing of the product in Ireland.

Mock-ups should comply with the following requirements:

- Mock-ups should be in colour.
- Where there is a range of pack sizes, only a representative mock-up of the smallest marketed pack size for each strength and dosage form need be provided.
- There should be no adverse effect on the readability of the text on other pack size labels. The text should be the same on all pack sizes, with the sole exception of a statement regarding pack size/number of units.
- In the case of additional product strength, a sample of the label of the existing strength(s) should also be submitted for comparative purposes.
- The particulars appearing on the label of all medicinal products should be printed in characters of at least 7 points Didot (or a size where the lower case 'x' is at least 1.4 mm in height, leaving a space between lines of at least 3 mm). The particulars appearing in the leaflet should be printed in characters of at least 8 points, as measured in font 'Times New Roman', leaving a space between the lines of at least 3 mm. For applications received after 1 February 2011, the particulars appearing in the leaflet should be printed in characters of at least 9 points, as measured in font 'Times New Roman', leaving a space between the lines of at least 3 mm.
- Label mock-ups are required for all immediate and outer packaging, including, for example, ampoule, vial and blister strip labels.
- A colour code and an indication of scale would be useful.

The mock-ups must be a true representation of the final packaging, and the readability of the text as required by the directive must not be adversely affected by any print finishes used in the final packaging, e.g. the use of highly glossy or reflective surfaces or metallic print is strongly discouraged as such may adversely affect readability. Background colours or logos which adversely affect the readability of the text should not be used. Colour to highlight non-critical areas of product information, such as the number of tablets in a pack, could potentially be confusing and may detract from critical information such as the strength of the product. Colours should be chosen to provide a good contrast between the text and the background to assure maximum legibility and accessibility of the information. Different colours in the name of the product are discouraged since they may impact negatively on the correct identification of the product name. The use of different colours to distinguish different strengths is strongly recommended.

10.1.2 Submitting package leaflets

Both a mock-up of the package leaflet and a text-only version of the package leaflet are required on initial submission of the application. A 'text-only' version of the package leaflet is the provision of the text that appears on the leaflet using the QRD/CMD(h) template headings in Word format. The required national elements, e.g. PA holder should be included. The submission of a final mock-up of the package leaflet is not mandatory for final approval; instead a text-only version of the final package leaflet is required. The applicant may provide a mock-up of the package leaflet in addition to the required text-only version of the package leaflet, if available.

MA holders are advised of the following notable exceptions to the above:

Label/leaflet combinations style package leaflet:

A colour mock-up of the label/leaflet must also be provided in addition to the text-only version of the package leaflet.

Products without a separate package leaflet (as the leaflet information is on the packaging):

A text-only version of the label is required in addition to the mandatory colour mock-up for the label.

During the course of assessment, certain changes may be requested to the labels and package leaflet. In reviewing the amended texts, the assessor will focus on the revisions which have been made. If other changes have been made which were not requested, the applicant should clearly identify them and bring them to the attention of the assessor.

All changes requested and agreed during assessment should be incorporated into the final mock-ups of the labels and leaflet. These final mock-ups or text-only versions of the labels and leaflets will be requested when the draft schedule is sent to the applicant for comment. No other changes to any aspect of content, layout or design should be included other than those agreed during the assessment. Applicants do not have to sign and date mock-ups or text-only versions of labels and package leaflets, whether submitted electronically as a scanned version of the full colour mock-up or as a pdf document. The final mock-ups or text-only versions will be retained at the HPRA as the approved market pack and leaflet.

10.2 Mutual recognition/decentralised applications

Labels and leaflets texts are agreed during the MR/DCP procedure for new applications and major variations. Mock-ups of the label must be supplied to all Member States along with the application. Both a mock-up of the package leaflet and a text-only version of the package leaflet are required in the initial application. Text versions are agreed during the procedure and final label mock-ups, along with a text-only version of the package leaflet incorporating those changes and any national requirements, should be provided promptly with the applicant's

comments on the draft schedule. A HPRA declaration of compliance for Braille (see section 7) should also be submitted.

10.3 Variations and Article 61(3) notifications

Any proposed change to the approved labels and leaflet must be approved by the HPRA. If the changes are consequential on changes to the SmPC, revised labels and/or leaflets should be provided with the application to vary the SmPC. All other proposed changes not connected with the SmPC are submitted to the HPRA using the application form for Article 61(3) notifications. Continued compliance with any previously submitted Braille declaration should be ensured by the applicant or updated Braille declarations should be submitted.

Variation applications should be accompanied by one copy of either a scanned or pdf version of the approved colour mock-ups with changes highlighted and one scanned or pdf copy of the clean revised colour mock-ups. Text-only versions of the package leaflet with the proposed changes clearly highlighted and clean revised text-only versions should also be provided. Text only versions of labels may be submitted instead of mock-ups if the product is not marketed.

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

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:

- Moving location of batch number/expiry date on inner and outer packaging provided no other details are changed.
- Change in abbreviation for batch number and expiry date, provided proposed abbreviation is one recommended by Appendix IV Terms/Abbreviations for Batch Number and Expiry Date to be used on the Labelling of Human Medicinal Products (i.e. Batch number: Lot, Batch, BN; Expiry date: EXP).
- 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 text.
- Any change to a barcode, e.g. number on the barcode, that does not affect any other aspect of the labelling and does not change the location of the barcode.
- 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.
- Addition, deletion or change in foreign MA numbers and/or foreign MA holder details, which does not affect any other aspects of the livery layout and font size.
- Addition, deletion or change in the administrative information for an EU MS or the UK placed within the 'blue box', which does not affect any other aspects of the livery layout and font size.

- Change to the details for reporting of side effects in other Member States not affecting the details for reporting of side effects in Ireland (joint country package leaflets).
- Change/deletion of a product name in another Member State in section 6 of the patient information leaflet (MRP products only).
- Change in the details of a distributor/wholesaler/local representative.
- Change to the dimensions of a carton with no change in layout or font size of text.
- Relocation of Braille (with no change to text).
- Change to packaging code/internal reference code on packaging.
- Reorientation of a pictogram without any changes to the wording or meaning and with no impact on legibility.
- 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.
- Deletion of the MAH logo or trademark on the carton (but MAH still clearly identified).
- Change to the trademark statement on a carton/leaflet, e.g. if a statement is changed from 'Product X is a registered trademark of Company Y' to 'Product X is a registered trademark', and there are no other changes to the text.
- Placing a previously non-marketed pack size on the market, where the content, font size and appearance of the label text are identical to the marketed pack, apart from the contents by weight/volume/number of units.
- 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 outlined in section 9.7 of this guideline and the safety features labelling requirements outlined below are met.

Any and all other changes to product labels or package leaflets will continue to require a formal notification to the HPRA.

11 SAFETY FEATURES

In accordance with the *CMDh implementation plan for the introduction of the safety feature 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.

Medicinal products that have to bear a safety feature must comply with the revised QRD template, i.e. implement the standard statement on the unique identifier and its carrier under section 17 and 18 of the particulars to appear on the outer packaging or the immediate packaging if the medicinal product has no outer packaging. In the case of nationally authorised products where the QRD template may not be available, mock-ups can be provided.

In the case of medicinal products where the ATD is placed on the immediate packaging because there is no outer packaging and the ATD affects the container and its closure system(s), information on the ATD and how the ATD affects the container and its closure system(s) is required (sections 3.2.P.2.4 and/or 3.2.P.7 of the Notice to Applicants Volume 2B).

ANNEX 1 EXAMPLE OF MULTILINGUAL LABELLING

