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ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

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DRAFT
**GUIDELINE ON THE READABILITY
OF THE LABEL AND PACKAGE LEAFLET
OF MEDICINAL PRODUCTS
FOR HUMAN USE**

**Revision
September 2006**

Update according to Directive 2001/83/EC as amended by Directive 2004/27/EC

Introduction

Legal framework

All medicines are required by Community law to be accompanied by outer/inner labelling text and a Package Leaflet setting out comprehensive information which is accessible to and understandable by those who receive it, so that they can use their medicine safely and appropriately. The safe and correct use of all medicines depends on users reading the labelling and packaging carefully and accurately and being able to understand and act on the information presented.

According to Article 54, Article 55 and Article 59 of Directive 2001/83/EC medicinal products must be accompanied by outer or immediate packaging information (labelling) and a package leaflet. Article 58 allows for the omission of a package leaflet where all the required information can be directly conveyed on the packaging.

Article 56 of Directive 2001/83/EC requires that the label text shall be easily legible, clearly comprehensible and indelible.

Article 56a of Directive 2001/83/EC requires the name of the medicinal product to be expressed in Braille format on the packaging, and the marketing authorisation holder to ensure that the package leaflet is made available on request from patients' organisations in formats appropriate for the blind and partially-sighted.

Article 59(3) of Directive 2001/83/EC provides 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.

Article 61(1) and 8(3)(j) of Directive 2001/83/EC specify that one or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the competent authority at the time of marketing authorisation application. The results of assessments carried out in cooperation with target patient groups shall also be provided.

Article 63(1) requires that the labelling and package leaflet shall be provided in the official language of the member state where the product is placed on the market. Additional languages can be included provided the information presented is the same in all languages and it does not impact adversely on the legibility, clarity and comprehensibility of the text.

Article 63(2) of Directive 2001/83/EC requires that the package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in the official language or languages of the member state(s) in which the medicinal product is placed on the market.

This guideline is published in accordance with Article 65 of Directive 2001/83/EC, which provides for the development of guidelines concerning, amongst other things, the legibility of particulars on the labelling and package leaflet.

The guideline is intended to apply to all marketing authorisation procedures and to all medicinal products, including those available without prescription.

Purpose

The main purpose of this guideline is to ensure that the information on the label and package leaflet is accessible to and able to be understood by those who receive it, so that they can use their medicine safely and appropriately.

This guideline is written to assist applicants and marketing authorisations holders when drawing up the labelling and package leaflet and preparing the specimens or 'mock-ups' of the sales presentations.

The guidance sets out advice on the presentation of the content of the labelling and package leaflet (required in accordance with Title V of the Directive) and on the design and layout concepts which will aid the production of high quality information. It includes guidance on 'consultations with target patient groups' for the package leaflet, and provides references to guidance documents which can be used to ensure that the content of labelling and package leaflet meet the legal requirements and are presented in a consistent way. Taken together these will assist in the harmonisation of product information across all Member States.

The guideline also includes information on how the requirements for Braille can be met, as well as how to make the package leaflet available in formats suitable for the blind and partially sighted patients.

Finally, the guideline includes advice on the preparation of specimens or 'mock-ups' of the sales presentation and the package leaflet. As provided for in Article 8.3(j) of Directive 2001/83/EC, a mock-up of the outer and immediate packaging together with the package leaflet must be submitted to the competent authority for approval, before commercialisation of the product. A mock-up is a copy of the flat artwork design in full colour, presented so that, provides a replica of both the outer and immediate packaging provides a three dimensional presentation of the labelling text. This mock-up is generally referred to as a paper copy and not necessarily in the material of the sales presentation.

Chapter 1 Readability of the Label and the Package Leaflet

Section A The Package Leaflet

If the package leaflet is well designed and clearly worded, this maximises the number of people who can use the information, including older children and adolescents, those with poor literacy skills and those with some degree of sight loss. Companies are encouraged to seek advice from specialists in information design when devising their house style for the package leaflet to ensure that the design facilitates navigation and access to information. A balance will need to be achieved between the length of the resulting leaflet and the accessibility of the information contained within it.

1. Print Size and Type

- **Choose a font which is easy to read.** For large quantities of text such as found in package leaflets a serif typeface is preferred since the shape of the characters is easier to read. Most books are set in semi-bold serif typefaces whereas bold sans serif fonts are more often used for signs. Stylised fonts which are difficult to read should not be used. It is important to choose a typeface in which similar letters/numbers, such as “i”, “l” and “1” can be easily distinguished from each other.
- **Where practical your font size should generally be 12 point for the main body of the text and where practical a larger font size for headings is recommended e.g. 14 point.** Consideration should be given to using larger fonts where it is known that patients with visual impairment are likely to be using the package leaflet, for example package leaflets supplied with eye drops. For visually impaired patients the preferred font size should be between 16 and 20 (refer to Chapter 2 section 6).
- **The widespread use of capitals should be avoided.** The human eye recognises words in written documents by the word shape, so choose lower case text for large blocks of text. However, capitals may be useful for emphasis.
- **Do not use italic fonts and underlining** as such devices make it more difficult for the reader to recognise the word-shape.

2. Design and Layout of the Information

- All text should be set horizontally and the use of “justified” text (that is text aligned to both left hand and right hand margins) should be avoided; however this may be acceptable where column format is used (see below).
- Line spaces should be kept clear. The space between lines is an important factor influencing the clarity of the text. As a general rule the space between one line and the next should be at least 1.5 times the space between words on a line, where practical.
- Contrast between the text and the background is important. Factors like paper weight, colour of the paper, size and weight of the type, colour of the type and the paper itself should be considered. Too little contrast between the text and the background adversely affects the accessibility of the information. Therefore, avoid background images behind the text which will interfere with the clarity of the

information making it harder to read. The paper weight is important as show-through of text impairs legibility.

- A column format for the text can help the reader navigate the information. The margin between the columns should be large enough to adequately separate the text. If space is limited a vertical line to separate the information should be used. Important information should be kept together so the text flows easily from one column to the next. Consideration should be given to using a landscape layout which can be helpful to patients. Where a multi-lingual leaflet is proposed there should be a clear demarcation between the different languages used.

3. Headings

Headings are an important aspect of the written information and can help patients navigate the text if used well. Therefore, bold text for the heading, underlining or a different colour, may help make this information stand out. Same level headings should appear consistently (numbering, bulleting, colour, indentation, font and size) to aid the reader. The use of multiple levels of headings should be considered carefully, as more than two levels may make it difficult for patients to find their way around the leaflet. Using lines to separate the different sections within the text can also be helpful as a navigational tool.

4. Print colour

Readability is not only determined by print size. Characters may be printed in one or several colours allowing them to be clearly distinguished from the background. A different type or colour is one way of making headings clearly recognisable.

Contrast is important, and the relationship between the colours used is as important as the colours themselves. As a general rule dark text should be contrasted against a light background. But there may be occasions when reverse type may be used to highlight particular warnings. In such circumstances the quality of the print will need careful consideration and may require the use of a larger font or bold text. Reversed-out text is particularly difficult for older readers.

A different colour is one way of making headings or important information clearly recognisable. Red colour print should be reserved for very important warnings only

5. Syntax

- Some people may have poor reading skills, and some may have poor health literacy. Aim to use simple words of few syllables.
- Punctuation should be simple. Sentences should be no more than about 20 words. It is better to use a couple of sentences rather than one longer sentence, especially for new information.
- Long paragraphs can confuse readers, particularly where lists of side effects are included. The use of bullet points for such lists gives a more open approach. No more than five or six bullet points in a list are recommended.
- A list of bullet points should be short and should be introduced with a colon, with a single full stop at the end of the list. The list should begin with the uncommon and specific case, and end with the common or general case, unless this is inappropriate for the product. For example:

Tell your doctor if you are suffering from:

- pulmonary tuberculosis
- any allergies that affect your lungs
- any chronic lung condition.

6. Style

When writing, use an active style by placing the verb at the beginning of the sentence, for example:-

- '*take 1 tablet*' instead of '*1 tablet should be taken*','

- '*you must...*' is better than '*it is necessary ...*'

Give reasons when telling patients what action to take. Instructions should come first, followed by the reasoning, for example: 'take care with X if you have asthma –it may bring on an attack'.

“It” should be used rather than repeating the name of the product, as long as the context makes clear what the pronoun refers to.

Avoid repetition of information by cross-referring to information which is under another heading where this is appropriate.

Avoid abbreviations unless these are appropriate. When first used in the text, the meaning should be spelled out in full.

All technical terms should be translated into language which patients can understand. Consistency should be assured in how translations are explained by giving the lay term with a description first and the detailed medical term immediately after. On a case by case basis the most appropriate term (lay or medical) may then be used thereafter throughout the package leaflet in order to achieve a readable text. Make sure that the language used alerts patients to all the information relevant to him, and gives sufficient detail on how to recognise possible side effects and understand any action which may be necessary.

All main section headings will be included within the leaflet but sub-headings and associated text within the leaflet should only be included if these are relevant for the particular medicine. For example if there is no information in relation to excipients of known effect this section may be omitted from the package leaflet.

7. Paper

For long leaflets, paper size of A4/A5 is preferable because paper of these dimensions can most easily be turned over and followed in a user-friendly way and is also easier for the patient to put back into the pack. Paper weight should be no less than 40g/m². Thinner paper may be too transparent and thus difficult to read. Glossy paper reflects light making the information difficult to read, so choose uncoated paper.

8. Use of Symbols and Pictograms

The legal provisions within Article 62 of Directive 2001/83/EC permit the use of images, pictograms and other graphics to aid comprehension of the information, but these exclude any element of a promotional nature. Symbols and pictograms can be useful provided the meaning of the symbol is clear and the size of the graphic makes it easily legible. They should only be used to aid navigation, clarify or highlight certain aspects of the text and should not replace the actual text. Consultation of patients of all symbols will be useful to ensure the meaning is generally understood. Pictograms, symbols and graphics should not be misleading, confusing, or contrary to the standards of good taste and decency, and should not be promotional. If there is any doubt about the meaning of a particular pictogram it may be considered inappropriate. Particular care will be needed when symbols are transferred or used in other language versions of the leaflet and further user testing of these may be necessary.

9. Additional Information

9.1 Product ranges

There should, in principle, be a separate leaflet for each product of different quantitative strength and pharmaceutical form. However it may be useful to include information on the different strengths and pharmaceutical forms available; e.g. where achieving a recommended dose necessitates a combination of different strengths, or the dose varies from day to day depending on the clinical response. In such circumstances, other strengths and pharmaceutical forms with the same name can be included in the leaflet, provided that these other products have each of the following:-

- the same indication(s),
- the same posology,
- the same route of administration,
- the same contraindications, precautions, warnings and side-effects.

For leaflets associated with medicines authorised through the centralised procedure, guidance on this is provided from the EMEA website. <http://www.emea.eu.int/htms/human/qrd/qrdplt/2509002.pdf>

Within the package leaflet, it may also be useful to refer to other pharmaceutical forms; e.g. in the leaflet of a tablet which is unsuitable for children to explain that there is an oral solution for children.

9.2 Products administered by a healthcare professional

For a product administered by a health professional, information from the summary of product characteristics for the health professional (e.g. the instructions for use, amongst other things) could be included at the end of the patient leaflet in a tear-off portion, to be removed prior to giving the leaflet to the patient. Alternatively the complete summary of product characteristics could be provided in the pack along with the package leaflet.

For a product administered in hospital additional package leaflets may also be provided separately from the medicinal product package (in addition to the one provided in the pack) to ensure that every patient receiving the medicine has access to the information. When the package leaflet is provided separately, the marketing authorisation holder should take

appropriate measures to enable the hospital staff to provide the patient with the current version of the package leaflet.

10. Templates for the Package Leaflet

The templates provided in all EEA languages on the EMEA Website <http://www.emea.europa.eu/index/indexh1.htm> (Human Medicines - Application Procedures – Product Information Templates) reflect the items which must appear on the labelling and package leaflet of medicinal products according to Directive 2001/83/EC. They will help to ensure that the statutory information appears as intended by the Directive, and to ensure consistency in the information provided across a number of different medicines.

The use of these templates applies to Mutual Recognition, Decentralised and Centralised applications. For national applications, national templates may apply.

For applications in the Centralised Procedure, product information is to be presented in the mandatory format and lay-out (see “QRD convention” on the EMEA Website) using the electronic product information templates. When using these templates, reference should be made to relevant Community Guidelines, QRD Guidance and the “Annotated QRD Template” which can be found on the EMEA Website and which provides detailed guidance on how to complete each section.

Having used the templates provided, marketing authorisation applicants will still need to format the resulting text into the relevant full colour mock up of the package leaflet. Also applicants should remember that using the template does not guarantee compliance with Article 59(3) of the directive and consultations with target patient groups will still have to be carried out on the full colour mock of the package leaflet prior to submission.

Section B Recommendations for the Labelling

Labelling covers both outer packaging and inner packaging which may include a lesser set of particulars. Nevertheless, many of the principles of good practice in relation to outer packaging will apply equally to the labelling applied to small containers and other inner packaging components.

Labelling ensures that the critical information necessary for the safe use of the medicine is legible, easily accessible and that users of medicines are assisted in assimilating this information so that confusion and error are minimised. In preparing this guidance, it is acknowledged that different users of medicines require and use information differently. Those involved in the design of labelling and packaging components should ensure that the following sections are taken into account prior to submission to the competent authority as any deviations from this guidance may need to be justified. The recommendations on print size and type, layout and colour given in relation to the package leaflet (section A) are equally applicable to labelling and should be borne in mind in designing and laying out the required information on labels. In particular the information presented on small packs will need careful consideration so that the text is presented in as large a font as possible to reduce the likelihood of medication error. Additional requirements may apply in particular member states and applicants should check details given in the Notice to Applicants, Volume 2A, chapter 7.

General considerations

Labelling must contain all elements required by Article 54 of Directive 2001/83/EC or a lesser set of particulars where the provisions of Article 55 apply. Nevertheless, out of a total of 15 information items, certain items of information are deemed critical for the safe use of the medicine. These items are:

- name of the medicine and its strength
- total content (where relevant)
- route of administration

Where possible these should be brought together using a sufficiently large font on the pack and on immediate packaging in the same field of view to aid users.

1. Name of the Medicinal Product

Article 54(a) of Directive 2001/83/EC sets out what is required in relation to the name of the medicinal product: The full name of the medicinal product, with its strength and its pharmaceutical form, and, if appropriate, whether it is intended for babies should appear on the outer packaging (the carton) and on the immediate packaging to aid accurate identification of the medicinal product. Where the medicinal product contains up to three active ingredients, the common name(s) of these active ingredient(s) should immediately follow the invented name of the medicinal product on the outer packaging and the immediate packaging, unless the common name(s) is part of the name.

For requirements concerning Braille, see chapter 2.

2. Strength and total content

In some cases the packaging may need to contain information on the quantity per unit volume and also on the total quantity per total volume. The total quantity per total volume can be particularly important for safety reasons for injectable products and other medicines available in solution or suspension.

Different strengths of the same medicinal product should be expressed in the same manner: for example 250mg, 500mg, 750mg, 1000mg and NOT 1g. Trailing zeros should not appear (2.5mg and NOT 2.50mg). The use of decimal points should be avoided where these can be easily removed (i.e. 250 mg is acceptable whereas 0.25 g is not). The decimal point need not be centred, provided that if a full stop is used it is clearly visible. For safety reasons it is important that micrograms is spelt out in full and not abbreviated. However, in certain instances where this poses a practical problem which cannot be solved by using a smaller point size then abbreviated forms may be used, if justified and there are no safety concerns.

3. Route of administration

This should be as registered in the summary of product characteristics only according to the standard terms. Positive messages should be used; for example “For intravenous use only” and only standard abbreviations may be acceptable (i.v., i.m., s.c.). Non-standard routes of administration should be spelt out in full to avoid confusion. Some routes of administration will be unfamiliar to patients and may need careful explanation. This is particularly important when medicinal products are made available for self-medication.

4. Design and layout

Applicants/marketing authorisation holders must make best use of the space available to ensure that the critical / important information is clearly mentioned on prime spaces on the outer and immediate packaging, printed in a sufficiently large font. Consequently, company logos and pictograms (if accepted) may be presented where space permits in a discreet manner on the outer packaging and on immediate packaging units, provided it does not interfere with the legibility of the legislative text.

Use of a large font will be appropriate, although other factors may also be important in making the information legible. Consideration should be given to the line-spacing and use of white space to enhance the legibility of the information provided. For some small pack sizes it may not be possible to present all the critical information on one face. The use of innovative design of packaging to aid in the identification and selection of the medicinal product is encouraged.

Colours should be chosen carefully to ensure a good contrast between the text and the background to assure maximum legibility and accessibility of the information. Highly glossy, metallic or reflective packaging should be avoided, as this affects the readability of the information. Different colours in the (invented) name of the product should be avoided, whereas use of different colours to distinguish different strengths is strongly recommended. Similarity in packaging which contributes to medication error can be reduced by the judicious use of colour by marketing authorisation holders. The number of colours used on packs will need careful consideration as too many colours could be detrimental to patient safety. The use of innovative outer packaging design is regarded to be of particular importance where space is at a premium. Any colour used on the outer pack should be carried onto small containers to aid identification of the medicine.

All outer packaging must include space for the prescribed dose to be indicated and/or blue box information as required by Member States (Information provided in Notice to Applicants Volume 2A, chapter 7 section 10).

5. Templates for labelling

The templates provided in all EEA languages on the EMEA Website <http://www.emea.europa.eu/index/indexh1.htm> (Human Medicines - Application Procedures – Product Information Templates) reflect the items which must appear on the labelling and package leaflet of medicinal products according to Directive 2001/83/EC. They will help to ensure that the statutory information appears as intended by the Directive, and to ensure consistency in the information provided across a number of different medicines.

The use of these templates applies to Mutual Recognition, Decentralised and Centralised applications. For national applications, national templates may apply.

For applications in the Centralised Procedure, product information is to be presented in the mandatory format and lay-out (see “QRD convention” on the EMEA Website) using the electronic product information templates. When using these templates, reference should be made to relevant Community Guidelines, QRD Guidance and the “Annotated QRD Template” which can be found on the EMEA Website and which provides detailed guidance on how to complete each section.

Having used the templates provided, marketing authorisation holders will still need to format the resulting text into the relevant full colour mock up of the packaging.

6. Other Information

As foreseen by Article 57 of the Directive, a member state may ask for additional information to appear on the packaging concerning identification and authenticity of product, the legal category for supply and price. National rules will apply in these circumstances and details on the requirements for the “Blue box” are given in the Notice to Applicants, Volume 2A, chapter 7. These requirements are also set out in the Notice to Applicants Volume 2C, “Guideline on the packaging information of medicinal products for human use authorised by the Community”.

Section C Immediate Packaging

The guidance provided in section B above will apply (where relevant) to immediate packaging.

1. Blister Pack Presentation

For blister pack presentations it is important that the particulars remain available to the user up to the point at which the last dose is removed. Often it will not be possible to apply all the information over each blister pocket, consequently where a random display of the information is proposed it should frequently appear across the pack. In all cases it will be acceptable to apply the batch number and expiry date to the end of the blister strip. As it is technically possible applying this information to both ends of each strip should be considered. Where a unit-dose blister presentation is proposed all the information required for blister packs must appear on each unit dose presentation.

In addition, blister foils should be printed to ensure maximum legibility of the statutory information using a sufficiently large font.

Colour for the text and the font style, should be chosen carefully as the legibility of the text on the foil is already impaired due to the nature of the material. Where possible, non-reflective material or coloured foils should be considered to enhance the readability of the information presented and the correct identification of the medicine.

2. Small Containers

Where the labelling particulars set out in article 54 of Directive 2001/83/EC cannot be applied in full to the labelling of small containers, as a minimum the particulars set out in Article 55(3) of the directive should be applied. Other information required in Article 54 can be added where space permits. The criteria for small container status would normally apply to containers of nominal capacity of 10ml or less. However, other factors may need to be taken into account such as the amount of information which has to be included and the font size necessary to ensure the legibility of the information.

Innovative pack design will be of particular importance where space is at a premium (e.g. the use of wrap-around or concertina labels). Paper labels are recommended to increase the legibility of the information applied to for example ampoules.

Chapter 2 Specific Recommendations for Blind and Partially Sighted Patients

Directive 2004/27/EC – amending Directive 2001/83/EC - includes changes to the label and package leaflet requirements.

This guidance interprets the requirements for Braille on the packaging, and the requirements for the package leaflet to be made available in formats for the blind and partially sighted according to Article 56a.

Legal text:

Directive 2001/83/EC as amended by Directive 2004/27/EC, Article 56(a)

“The name of the medicinal product, as referred to in Article 54 a must also be expressed in Braille format on the packaging.

The marketing authorization holder shall ensure that the package information leaflet is made available on request from patients’ organisations in formats appropriate for the blind and partially-sighted.”

Directive 2001/83/EC as amended by Directive 2004/27/EC, Article 54(a)

“The name of the medicinal product, followed by its strength and pharmaceutical form, and if appropriate, whether it is intended for babies, children or adults; where the product contains up to three active substances, the international non-proprietary name (INN) shall be included, or, if one does not exist, the common name.”

Implementation

The provision of Article 56a will apply after the end of the implementation period – 30 Oct 2005 – to all medicinal product approved after this date. It will not apply immediately to products authorized before 30 October 2005.

Nevertheless companies are encouraged to apply the provision to all medicinal products as soon as possible. For specific implementation requirements reference is made to the relevant national legislation and EMEA guidance for Centrally Authorised Products.

Braille

Braille is the internationally widespread reading and writing system for blind and partially sighted people. The system was founded in 1825 by Louis Braille (1809 –1852), who lived in France and himself was blind. Braille is not a language, it is just another way to read and write a language.

Braille consists of arrangements of dots which make up the letters of the alphabet, numbers and punctuation marks. The basic Braille symbol is called the Braille cell.

Due to the reason that there are differences in Braille in different countries, the type of Braille letter (size of Braille cell) has to be standardized. The use of Marburg Medium is highly recommended.

The uncontracted Braille system should be used. In this system every Braille character (Braille cell) makes up the letter of the alphabet, punctuation mark, numbers, etc. The

contracted Braille system with letter-combinations should not be used, except in small volume packaging (up to 10 ml volume) – see paragraph below under “Scope”.

Scope

“The name of the medicinal product, as referred to in Article 54a” should be interpreted in a way which allows clear identification for blind people. According to the definition in Article 1.20 of Directive 2001/83/EC as amended “the name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorization holder”, the (invented) name of the medicinal product followed by its strength should be put in Braille on the packaging of the product.

For medicinal products authorised only in a single strength, it is acceptable that only the invented name in Braille is put on the packaging.

This interpretation does not prevent companies to express further information

(pharmaceutical form, and if appropriate, whether it is intended for babies, children or adults, etc) in Braille on bigger volume packages on a voluntary basis. Also the inclusion of the expiry date in Braille would be welcome, although it is acknowledged that this may not always be feasible.

For Herbal Medicinal Products the Braille requirement will be restricted to the invented name of the Medicinal Product only. Where the name consists of the active substance(s), information could be limited to the plant name (+ plant part in those cases where several parts are available), plus the type of preparation and the strength in those cases where several strengths exist.

In case of small volume packages (up to 10 ml) with limited space capacity, alternative means of providing Braille information may be considered, eg. use of contracted Braille system or certain defined abbreviations or addition of supplementary “tab” label. Particular consideration should be given to medicinal products likely to be used by a high visually impaired target population, eg. certain eye drop preparations.

In case of multilingual packaging, the name in Braille has to be printed in all the different languages concerned. Companies are encouraged to use the same invented name for the same medicinal product.

There is no need to put the name in Braille on the packaging of products which are only intended for administration by health care professionals, for example it is not required to put the name in Braille for vaccines.

Packaging

The name in Braille does not have to be printed on the immediate packaging - such as blisters, ampoules and bottles it only has to appear on the outer/secondary packaging, which is normally a carton. In case where there is no secondary packaging, e.g. large volume bottles (500 ml, 1000 ml, etc.), it is possible to fix an adhesive Braille label around the bottle during the manufacturing process.

On a voluntary basis companies can put the name in Braille on all packaging components.

Affixing an adhesive Braille label at the point of sale/dispensing of the medicinal product on request is not recommended, due to the risk of affixing the wrong Braille label and confusion.

Concerning the location of the Braille on the outer packaging there is no need to put the Braille dots on an empty space of the packaging, but the underlying printed text has to be easily legible.

Where Braille is present on the (outer) packaging of a medicinal product, parallel importer/parallel distributor should ensure that the same Braille text is provided in the language(s) of the member state of destination and that the original Braille text will not cause confusion.

Package information leaflet for blind and partially sighted

On request the package leaflet should be provided for partially sighted people in a suitable print, taking into consideration all aspects determining the readability (eg. Fontsize: 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.). In certain cases the appropriate format may be the package leaflet available in Braille.

Choice of the appropriate medium should be made by the marketing authorisation holder in consultation with representatives of organizations for the blind and partially sighted. It is the responsibility of the marketing authorization holder to provide the package leaflet on request from patients' organizations in an appropriate format and to ensure that the current version is supplied.

These requirements concerning the package leaflet for blind and partially sighted persons also fully apply to parallel importers/distributors.

Chapter 3 Guidance concerning consultations with target patient groups for the package leaflet

1. Introduction

According to Articles 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC new requirements apply to the package leaflet. Article 59(3) as amended requires that consultation with target patient groups ('user consultation') be carried out to demonstrate the readability and usefulness of the package leaflet to patients.

Article 59(3) reads:

"The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use."

Article 61(1) states that :

"The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority."

Article 63(2) states that:

"The package leaflet must be written and designed to be clear and understandable, enabling the user to act appropriately"

In addition Article 28(2) and (3) of Directive 2001/83/EC requires that products authorised through the mutual recognition and decentralised procedures will result in a harmonised package leaflet between Member States.

2. Scope

For all marketing authorisations granted after 30 October 2005, all the requirements set out in Directive 2001/83/EC as amended apply. Therefore all package leaflets included in Community or national marketing authorisations have to be checked accordingly and the information about the patient consultation must be included in the application dossier.

Further guidance is given in section 8 of this guideline.

For changes to existing marketing authorisations, the need for user consultation covers in principle situations where significant changes are made to the package leaflet, either through a variation or a procedure according to Article 61(3) of Directive 2001/83/EC.

3. Forms of patient consultation

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

They do not define the precise method to be used. As a consequence, these provisions permit user testing as well as other appropriate forms of consultation.

3.1 User Testing

One of the possible ways of complying with the new legal requirement is by performing a 'user testing' of the package leaflet.

User testing means to test the readability of a specimen with a group of selected test subjects. It is a development tool which is flexible and aims to identify whether or not the information as presented, conveys the correct messages to those who read it. Testing itself does not improve the quality of the information but it will indicate where there are problem areas which should be rectified. The user testing should be part of Module 1 of the application dossier.

3.2 Other methods

Other methods than user testing may be acceptable provided that the outcome ensures that the information is legible, clear and easy to use so that patients can locate important information within the package leaflet, understand it and enables the user to act appropriately. Such alternative methodology will have to be justified by the applicant/marketing authorisation holder and will be considered on a case-by-case basis.

4. Demonstration of patient consultations

In general, performing the user testing or another justified consultation method will be essential prior to granting or varying any marketing authorisation under either the centralised, mutual recognition, decentralised or national procedures.

Member States and the European Medicines Agency agreed on harmonised Quality Review of Documents (QRD) templates for the package leaflet to ensure that the statutory information appears as intended by the Directive 2001/83/EC. Compliance with the QRD templates does not exempt from the obligation to undertake a user test or other form of user consultation.

a) New consultation for a medicinal product

In the following situations a user consultation is always required:

- First authorisation of a medicinal product with a new active substance,
- Medicinal products which have undergone a change in legal status,
- Medicinal products with a new presentation,
- Medicinal products with particular critical safety issues.

b) Reference to already approved package leaflets according to Article 59(3) and Article 61(1) of Directive 2001/83/EC

The evidence from tests on similar package leaflets may be used where appropriate. Examples of when this may be considered acceptable based on a sound justification by the applicant/marketing authorisation holder are:

- extensions for the same route of administration e.g. intravenous/intramuscular or oropharyngeal/laryngopharyngeal,
- same safety issues identified,

- same class of medicinal product.

It may be appropriate for an applicant/marketing authorisation holder to refer to a representative sample of package leaflets for medicinal products which comply with the new legislative requirements. The types of package leaflets should be chosen carefully to be representative of one or more of the following considerations:

- recently approved package leaflets for a corresponding medicinal product,
- reflect complex issues of risk communication which may need careful handling,
- medical terminology which requires detailed explanation .

However, certain package leaflets may require further user consultation to provide reassurance that patients will benefit from the information provided. This is e.g. the case where user consultation concentrates on one particular aspect of a leaflet which may need particular patient attention, e.g. expression of risk of side effects or complex instructions how to administer the medicinal product.

5. Testing of multiple language versions

The package leaflet should be legible, clear and easy to read in all EEA languages. As a matter of principle it is normally sufficient to undertake patient consultation in one EEA language. Results of such consultation should be presented in English for the centralised, decentralised and mutual recognition procedure, or in the national language for national procedures to permit the assessment of the test to be undertaken by competent authority responsible for granting the marketing authorisation.

In the centralised, decentralised and mutual recognition procedure, only the English language version of the package leaflet will be agreed during the scientific assessment.

The quality of translation should be the focus of a thorough review by the applicant/marketing authorisation holder once the original package leaflet has been properly tested and modified.

During the drafting of the original package leaflet every effort should be made to ensure that the package leaflet can be translated from the original to the various national languages in a clear and understandable way. It is important that the outcome of the user consultation is then correctly translated into the other languages. Strict literal translations from the original language may lead to package leaflets which contain unnatural phrases resulting in a package leaflet which is difficult for patients to understand. Therefore, different language versions of the same package leaflet should be 'faithful' translations allowing for regional translation flexibility, whilst maintaining the same core meaning.

Following the grant of the marketing authorisation, the responsibility for the production of faithful translations will rest with the marketing authorisation holder in consultation with the Member States/European Medicines Agency.

If user consultation has been performed on a package leaflet in the old QRD template, there is no need to be retested when updating according to the new QRD template.

6. Presentation of results

The presentation of results should be shortened to a summary explaining how the consultation was executed and how the resulting package leaflet accommodated any need for change. The summary should be in Module 1.3.4 of the application and should have the following structure:

1. Product description
2. Consultation or test details, such as:
 - Method used
 - Explanation on the choice of population consulted
 - Language(s) tested
3. Questionnaire (including instructions and observation forms)
4. Original and revised package leaflets
5. Summary and discussion of results (subjects' answers, problems identified and revisions made to relevant package leaflet section)
6. Conclusion

All other details should be available on demand.

The report and the results of the consultation should be presented in English for the centralised, decentralised and mutual recognition procedure or in the national language for national procedures.

7. Approval by the competent authority

In approving package leaflets the competent authorities will look for evidence that people who are likely to rely on the package leaflet can understand it and act appropriately. Any consultation submitted in support of a package leaflet will need to cover the following:

- Data gathered from users under defined conditions
- The people who are likely to rely on the package leaflet for a particular medicine will depend upon a number of factors and may include carers (e.g. parents, partners, friends, as well as nursing assistants) rather than patients if the medicine is generally intended for administration by someone other than the patient.
- In order to ensure that those involved can understand and apply the information, the evidence presented must demonstrate that they can pick out the relevant information, interpret this and describe the action they would take as a result.
- The key information will need to be defined prior to the consultation by the marketing authorisation holder and is likely to include significant side effects, warnings, what the medicine is for and how to take/use the product.

8. Other issues for consideration

The Member States or the European Medicines Agency will have considered other aspects in relation to consultation or user testing and usability of package leaflets and additional guidance is available or under development concerning:

- Timing of user consultation, submission and assessment within the evaluation procedure;
- Guidance in relation to usability and presentation of information;
- Guidance on how user testing should be carried out and what alternative methods are acceptable.

An example of one way in which consultation with target patient groups could be carried out is included in annex1.

Annex 1

ILLUSTRATION - One Way of Undertaking a Test of a Package Leaflet

This information is included for illustrative purposes only and is an example of a method that could be used for consultation with target patient groups.

The method described covers one-to-one, face-to-face, structured sets of interviews, involving at least 20 participants reflecting the population for whom the medicine is intended¹. As indicated above, other performance-based methods are equally valid, and competent authorities will judge applications on a case by case basis.

1. Performing the test

- Testing of Package Leaflets may be done by the MA holder or a suitably qualified company on its behalf.
- It should be carried out by an experienced interviewer with good interview, observational and listening skills.
- Ideally the writer of the Package Leaflet will carry out the interviews, or occasionally accompany the interviewer during testing, to enable direct transfer of learning.

2. Recruiting Participants

- Ensure a range of different types of people who are able to imagine needing to use the medicine.
- If the medicine is intended for a rare illness, then where possible test the leaflet among people who actually have or have had the illness. You may need to exclude people who have previously taken or are currently taking the medicine.
- Remember that information which can be used by the least able will be beneficial for all users. Try and include:
 - particular age groups such as young people and older people – especially if the medicine is particularly relevant to their age group
 - new users or people who do not normally use medicines, particularly for information provided with new medicines likely to be used by a wide range of people (e.g. analgesics or antihistamines)
 - people who do not use written documents in their working life
 - people who find written information difficult.
- Recruit participants from wherever is most relevant and practical. For example you could use:
 - older people's lunch clubs

- self-help groups
- patient support groups
- community centres
- parent and toddler groups.

3. **Sample Size and Use**

- Only small numbers of participants are needed. The aim is to meet the success criteria in a total of 20 participants. The important thing is not to re-test participants whom you have already tested. You can achieve this by undertaking:
 - A pilot of around 3-6 participants to test that the questions will work in practice. As you gain experience, you may be able to use just two or three participants in the pilot test.
 - Next, at least two rounds of 10 people each, reviewing the results after the first round and making any necessary amendments to the Package Leaflet
 - Repeat tests until you have satisfactory data from a group of 10 participants
 - A final test of a further 10 to see if the success criteria are also met in this further 10 (i.e. in 20 participants in total).

4. **Success Criteria**

A satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the Package Leaflet, of whom 90% can show that they understand it.

If you use a different method of testing, different success criteria may be appropriate. Competent authorities will consider these on a case-by-case basis.

5. **Test Protocol**

- You are advised to:
 - Draw up a new protocol for each product
 - Include questions that address all the important and difficult issues, and use rigorous assessment criteria
 - Include a set of expected correct answers
 - Design the test to last no more than 45 minutes, to avoid tiring participants
 - Ensure that the questions reflect any specific issues for safe and effective use and compliance issues related to the medicine being tested. Testing is most beneficial when the questions relate to areas where patients' fears are greatest, such as side effects. Avoiding serious safety issues with a medicine during user testing of the Package Leaflet would invalidate the test.

- The interviewer should:
 - Use a written set of questions for reference
 - Ask the questions orally
 - Adopt a conversational manner, allowing ample opportunity for interaction with the participant
 - Ask participants, once they have located the required information, not to repeat it parrot-fashion but to put it into their own words where appropriate.
 - As well as recording the answers to the questions, observe how each participant handles the leaflet and searches for information, noting, for example, whether people become lost or confused. This will yield valuable information about how to improve the structure of the Package Leaflet.
- The questions should:
 - Adequately cover any critical safety issues with the medicine.
 - Be kept to a minimum; usually 12 -15 will be enough, though more may be required in special cases, e.g. if there are significant safety issues to be investigated
 - Cover a balance of general and specific issues. A general issue might be what to do if a dose is missed, while a specific issue might relate to a side effect that occurs particularly with that medicine.
 - Be phrased differently from the text of the leaflet to avoid “copy-cat” answers, based merely on identifying groups of words
 - Appear in a random order (i.e. not in the order the information appears in the leaflet).

Copies of the protocol(s) including the questions asked, the responses offered, the interviewer’s written observations and the different versions of the Package Leaflet tested must be submitted to the competent authority for review.