



Making Medicines Affordable

POSITION PAPER

POSITION PAPER ON THE DRAFT GUIDELINE ON THE READABILITY OF
THE LABEL AND PACKAGE LEAFLET OF MEDICINAL PRODUCTS FOR
HUMAN USE, REVISION SEPTEMBER 2006

OCTOBER 2006



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EXECUTIVE SUMMARY

EGA welcomes the opportunity to comment on the “Draft guideline on the readability of the label and package leaflet of medicinal products for human use, revision September 2006”. Feedback is provided in the form of this Position Paper, and also as a “Table of Comments”, which should be read together.

The update in the guideline is welcome although it comes one year after the changes in legislation following the Pharmaceutical Review. It comes with a year of “reactive” experience where the User Testing of Package Leaflets has put a heavy burden on the Generic Industry and the Regulatory Authorities. In the past 12 months there has been confusion over what is required, when, and how to assess the reports which have been submitted. Assessment has been slow, and there has been insufficient feedback. Many generic companies make at least one or two MA applications per month, if not more, and so there are many User Tests in the system.

The introduction of user testing for applications using DCP and MRP has had a large impact on generic companies, and there is a need for standardisation across Europe in the assessment of these tests by the different Regulatory Authorities. The requirement for User Tests has delayed applications, particularly of outgoing MRPs on already authorised National Marketing Authorisations and Repeat Use MRPs.

The first major concern is updating sections of the existing Guideline, which in our view, did not require revision.

Firstly, the section on Print Size and Font (Chapter 1 Section A 1 Print Size and Type) does not need rewriting. The 1999 version of the Guideline Section A (1) is well written and addresses the size of the type for both the Label and Package Leaflet in a practical way. The Guideline needs to be in the “real world” and understand the practical difficulties in fitting a large amount of required Regulatory text onto a package leaflet. The suggestion of moving the required font size from 7 or 8 point, which is reasonable, to 12 point, which is totally unreasonable, is completely impractical. Particularly when there is provision in the legislation which ensures that visually impaired people can receive the Package Leaflet in large print on request.



Secondly, we have major concerns on the proposed change to tighten the requirements for a “pass” of User Testing. There is no justification for this and the requirement of the previous guidance should be used (16/20). Meeting the test requirements in the existing guidance is already challenging, and therefore we request there is no tightening of the test requirements until Industry and Authorities have gained more experience. Tightening of the requirements should only come when experience indicates that it is required to ensure the safe use of medicines in patients.

The Generics Industry would like to work together with the authorities to provide Patient Information in a way that contributes to the safe and correct use of medicinal products. The generics industry is willing to co-operate to ensure that every time a patient opens a pack of medication, they receive the same leaflet in format and language irrespective of the manufacturer. Therefore proposals for work-sharing such as following the IBD initiative, the initiative in the UK or introduction of Leaflet Templates by Therapeutic Group will ensure that resources of MA Holders and Regulatory Authorities are channelled into ensuring the approval and supply of good quality, understandable and accessible Package Leaflets and Labelling.

This update is an opportunity to learn from this experience and arrive at very clear practical guidance. The large number of companies who have commented and the large number of comments - suggest that there needs to be more revision before this Guideline can address the needs of Regulatory Authorities and Industry now.

The overall aim of the guideline should not be lost (this quote is from the current version); and should be included in the Guideline Revision under “Purpose” page 2.

“Ensuring the label and package leaflet are readable is the primary objective of this guideline. It may be therefore acceptable for a package leaflet, which achieves an acceptable level of performance in a readability test to deviate from the rest of the guideline”.

1. General Comments

It is unclear from the guidance how the provisions will apply to Marketing Authorisations granted before October 2005, and what situations would trigger a User Test. The wording “significant changes are made to the package leaflet” requiring User Testing is not helpful. Experience with User Testing has shown that the most important factors are the layout and the formatting used - not the wording of the leaflet. Therefore this should be changed to “significant changes to the layout and format of the package leaflet”. The mechanism for approval is either a “variation or a procedure according to Article 61(3) of Directive 2001/83/EC”, the requirement for Art 61(3) submission is that the change is not connected to a change in the Summary of Product Characteristics. It is proposed that submission of a User Test report should be a Type 1 variation (cross-reference to Variations revision).

In view of the large number of nationally authorised generic MAs for older molecules it would be appreciated if Competent Authorities can agree to mutually recognise a positive assessment of a User Test in another member state. This would save resources in



reassessment of the same user test by different authorities, and also ensure a consistency in the outcome of assessment. For this reason it is also proposed below, that User Tests for National MAs can be conducted either in English or in the local language.

There needs to be agreement on how User Tests for drugs in the same therapeutic class e.g. ATC level 3 can be bridged. It would be helpful to include guidance on bridging in this revised guidance. There needs to be some flexibility as companies have large number of national authorisations, and the ideal would be to share User Testing results for one molecule or third level ATC code throughout Europe. In order to be efficient with resources, it is proposed that once a User Test has been approved by one Regulatory Authority, that approval is recognised throughout the EU.

Additionally if it is clear from an EPAR or PAR that a package leaflet has passed User Testing, other applicants may follow the same test and format, and obtain an exemption to repeat User Test by cross-reference to the relevant (E)PAR document. This would be desirable for patient safety, especially when a patient is switched from a branded product to a generic product, as the advantage is that the patient would receive the same information in the same format and layout.

Early experience of the QRD template and User testing has shown that there is a need to introduce additional headings under the required headings to make the leaflet more understandable. This is permitted when using the template. If user tests repeatedly show that the QRD template is a format which is not logical to the general population, consideration should be given to revise it in the light of experience, or allow MA holders to deviate from it, should that be the outcome of the User Test. Also there should be a mechanism in place to be able to feed back comments from User Testing on the QRD template, so that the template can be updated and revised.

Specific Comments - with reference to Sections of the Revised Guideline

2. Purpose

2.1 Purpose should include guidance for assessors in Competent Authorities

The purpose of the Guideline should also be to assist Competent Authorities to apply a consistent approach when assessing and approving “mock-ups” of labelling and leaflets. This purpose should be added to paragraph two.

It is clear from the Press Release (EMEA/457658/2006) dated 15 November 2006 that “the EMEA and CMD(h) have recently concluded that further experience was necessary in order to develop guidance for assessors involved in the assessment of user consultations and for industry”. This quote should be added to the Guideline.

2.2 Specimens and Mock-Ups, and consistency with other guidance

“Specimens” are referred to in this text without definition. Specimens and Mock-Ups have been defined in other recent draft guidance “Revised Checking Process of Mock-



Ups and Specimens of outer/immediate labelling and package leaflets in the Centralised Procedure” as:

“A `mock-up' is a copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the **outer** and **immediate** packaging so that the three dimensional presentation of the label text is clear.

A `specimen' is a sample of the actual printed **outer** and **immediate** packaging materials and **package leaflet** (i.e. the sales presentation)”.

It is suggested that the definitions in different Guidance documents are consistent, the definitions used in Notice to Applicants are preferred. All references to specimens should be removed from the Readability Guideline. Specimens, as defined above, should only be required after a Marketing Authorisation or Variation to change the labelling or package leaflet has been approved. A specimen should be supplied to Competent Authorities, post-marketing, on request, for their information only.

Consideration should be given to add a glossary of terms used in the guidance, and this should be consistent with other guidance (draft and in force) including QRD templates. The UK has published a “Glossary of Medical Terms in Lay Language” in Annex 8, of the Document entitled “Always read the leaflet - Getting the best information with every medicine”. This could be used as a starting point for a Glossary in the English Language.

3. Chapter 1 Section A The Package Leaflet

3.1 Print size and Type

- A font which is easy to read

The current “Guideline on the readability of the label and the package leaflet of medicinal products for human use” states that the “the type of print chosen should be such as to ensure maximum legibility. The draft guideline has made the suggestion that a “serif typeface is preferred”. This is an area where there is debate, and there in fact, there is no conclusive evidence that serif fonts are more readable than sans serif fonts. The font is a matter of personal preference. Generally, the most legible typefaces are those which the reader is accustomed to, and so there will be inter-individual preferences depending on what reading material is read. The example given that the guideline that i, l and 1 should be easily distinguished are not actually easily distinguished with the selected font, and a better example should be shown. Therefore it is suggested that this section of the guideline remains unchanged.

- Font Size

The current “Guideline on the readability of the label and the package leaflet of medicinal products for human use” states that “the particulars appearing on the label of all medicinal products, should be printed in characters of at least 7 points



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Didot (or of a size where the lower case “x” is at least 1.4 mm in height), leaving a space between the characters of at least 3 mm. The particulars appearing in the leaflet should be printed in at characters of at least 8 points Didot, leaving a space between the lines of at least 3 mm. Examples of the different point sizes were given.

The author of the previous guidance appreciated that Point size only has any meaning if quoted with a particular font, or height of a character and that equally important, if not more important factor in the readability of printed texts are the spaces between the lines (this is known as the leading).

The different sizes of fonts can be illustrated by using the same point size for the different fonts, it can be seen that the actual size of the text, (the height of characters) and the spacing varies considerably e.g.

Serif Fonts

This is written in Times New Roman 12 pt,
This is written in Courier New 12 pt
This is written in Georgia 12 pt,
This is written in Century Schoolbook 12 pt.

Sans Serif Fonts

This is written in Arial 12 pt,
This is written in Comic Sans MS 12 pt,
This is written in Tahoma 12 pt,
This is written in Verdana 12 pt.

This illustrates that the size of the text, and therefore ease of reading, is dependant on both the font type and the point size. It is meaningless to quote point sizes in isolation.

The artwork department of Pharmaceutical Companies select the largest font size in relation to the amount of text which needs to be fitted in the package leaflet, and should the results of User Testing demonstrate that fonts of smaller point can be read and understood, there should be no requirement to specify point size upfront. In order to fit the information required onto a page, experience has shown that point sizes of 6, 7 and 8 have to be used for some fonts (obviously the size of text which results depends on the font used), in order to fit all the required information onto an A4 sized leaflet.

MA Holders are obliged to provide larger print texts, on request, to those with visual impairment or have difficulty reading a small print size. It should be borne in mind that most of the type we read everyday is 8 pt or below.



Consumers who have concerns about the packaging and environmental impact on waste, frequently provide feedback about the waste in the leaflet and other packaging. Therefore there is a tension about the size of the Package Leaflet in terms of readability and the concerns about the use of paper and the impact on the environment, particularly where the Package Leaflet has to include the information in more than one EU language.

Therefore it is suggested that the previous version of the guideline should remain, as it linked the font type with the point size, and also indicated in the same section the importance of the spacing or leading between the lines of text (this is referred to later in the draft guideline, under Design and Layout of the Information but uses a completely impractical suggestion of 1.5 spacing).

- Widespread Use of Capitals

Agree that text in CAPITALS should be used sparingly and where needed for emphasis, this has been apparent from the results of User Testing.

- Italics and Underlining

There is inconsistency in the draft guidance, as on page 1 the text states “Do not use italic fonts and underlining as such devices make it more difficult for the reader to recognise the word-shape”, whereas on page 2 under **3. Headings** the text states “Therefore, bold text for a heading, underlining or a different colour may help make this information stand out”.

It is suggested that the reference to underlining on page 1 is removed, in order to have consistency within the guideline. Additionally, if user testing indicates that italic fonts are helpful, then they should be allowed.

3.2 Design and Layout of Information

User Testing of Package leaflet has shown that the layout, including keeping sections together, is important in ensuring that the consumers find information. This should be mentioned, as well as some of the lessons learned from testing experience so far.

Space between one line and the next of 1.5 is rarely practical and so this suggestion should be removed. Newspapers which most readers read every day do not have this spacing or leading.

3.3 Headings

The headings in the QRD template (which there is an obligation to use) need to be reviewed as they could be much better expressed in some languages.



3.4 Print Colour

Newspapers and books are printed in black on a white background, it is anticipated this is how most of the population receive printed information. Therefore the usual standard is anticipated to be what people are used to; black print on white paper. Colour may be used to make headings more prominent or differentiated from the body of text.

3.5 Syntax

The updated guideline suggests that sections for side-effects are described by lists using bullet points, and recommends that there are no more than 5 or 6 bullet points in a list. The previous guidance stated “there should be no more than nine items where the bullet points are simple and no more than five for when they are complex”, For most Package leaflets, the number of side-effects which have to be listed (and sometimes explained) would make this change from nine to 5/6 impossible. The guidance should reflect the reality of the situation faced by authors, and make alternative suggestions for dealing with a very large number of side-effects. These can be divided by frequency (not so easy to obtain these data for old established products) or by organ, system, class. Alternatively a side-effect which is very serious can be at the start of the section, particularly if there is immediate action the patient needs to take, should they experience this side-effect.

It would be helpful if more guidance on dealing with the side-effects is given in this section, as experience to date is that different competent authorities have different preferences in the side-effects part of the Package Leaflet, making one harmonised package leaflet across the EU very difficult to achieve. Reference could be made to the guidance from the MHRA “Guidance on the Communication of risks and benefits in PIL”, which clearly describes how to present Section 4.8 of SmPC to the patient. This Section is a key section of the Package Leaflet and the patient should know exactly where they stand with regard to the potential serious side-effects and their symptoms, and what actions need to be taken such as go immediately to hospital.

Specifically, when using the QRD template, some competent authorities have asked for side-effects to be in order of organ, system, class (MedDRA type organisation) whereas others, have required it to be in order of frequency. Agreement needs to be reached on this point and included in this guidance. It is known from experience that MedDRA system organ class are not easily understood by the majority of patients.

3.6 Style

It has been found in User Testing it is necessary to repeat warnings in more than one section, and asking the reader to cross-refer to different sections and navigate around the PIL is not helpful. It takes them time to locate the section, and users associate particular information with particular headings. Therefore we disagree with the point that repetition of information should be avoided, and information should be cross-referenced.

3.7 Paper

The previous guidance did not have the statement “Glossy paper reflects the light making the information difficult to read, so choose uncoated paper”. Manufacturers should be free to select the paper type suitable to their packaging machinery which represents a significant investment (over one million euros).

3.8 Additional Information

- Product Ranges

There is no need for a separate leaflet for different quantitative strength of a product with the same pharmaceutical form. Therefore section 9.1 should be reworded to reflect reality, that it is the **usual case** that product ranges are combined onto one leaflet, given the conditions quoted.

- Products Administered by a healthcare professional

It would be useful to include some guidance on the level of detail required for a product administered by a healthcare professional - details of the dose information are less important, and patients should be guided to speak to the doctor or nurse (not the pharmacist). The use of the leaflet in hospitals is very different from use in the community and some further guidance on the content of a package leaflet for use in a hospital setting would be helpful.

3.9 Templates for the Package Leaflet

The guidance directs the applicant towards the QRD templates which are available on the EMEA website. As these are used in MRP, DCP and CP, applicants would also like to use these for national applications as well. Therefore use of national templates, where they exist, should only be optional for the applicant, and they should also be able to use the QRD template if so wished.

It would be an opportunity to introduce Templates for different categories of drugs, and to place them on the web, so that all applicants could use (if they wished) the same Template. Once the template has passed User Testing, any applicant choosing to use it, need not repeat User Testing i.e. it would be exempt. The advantage of this approach is that every patient would receive very similar leaflets in terms of layout and content, irrespective of manufacturer. This would assist in the safe use of medicines (central to the Legal Framework on page 1).



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Under templates, it would be useful to note that full colour mock-ups are often in black and white. Package Leaflets for generic medicinal products are often printed black text on a white background.

4. Chapter 1 Section B Recommendations for the Labelling

In some European countries the decimal place is signified by a comma and not a full stop, the guidance in Section 2 should reflect this, and any other national differences in the expression of numbers.

5. Chapter 2 Specific Recommendations for Blind and Partially Sighted Patients

It may be helpful to include the reference to the Marburg Medium, for those readers not familiar with Braille.

“The System of the German Braille” (Das System der Deutschen Blindenschrift) 3rd edition published by the “Deutsche Blindenstudienanstalt e.V.” Marburg, 2001.
ISBN 3-89642-011-9

6. Chapter 3 Consultation with User Groups

6.1 Other Methods

The following alternative methods are proposed;

- 1) Package Leaflet Templates for drug classes:

The QRD template is already well-structured, and it is proposed that Industry and Authorities work together to produce Templates for different drug classes. The concept that all manufacturers can share the same format and content of Package Leaflet for the same Medicinal Product, would be very useful in ensuring that the patient receives the same information every time they are supplied with the product, and this would increase patient safety, and aid compliance. The results of the User Testing of the Templates could be shared, and so remove the need for the repeated testing of Package Leaflets.

This could be initiated by producing Template Package Leaflet for NSAIDs following the recent CMD(h) review.

- 2) Link in with the harmonised birthdate initiative



If the Initiative for the Harmonisation of International Birthdates works as envisaged, all MA holders for the same drug substance will submit PSURs to a Reference Member State at the same time, the outcome could be a harmonised SmPC throughout the EU (where one does not already exist). If only the side-effects section of the SmPC is harmonised, then taking this approach is less feasible, although it should be noted that the texts of SmPCs do not need to be identical for the result of User Tests on Package Leaflets to be valid. It would depend how many differences there were and whether this is material to the Package Leaflet.

If a sufficient number of sections of the SmPC is harmonised, this could in turn lead to a harmonised User Tested Package Leaflet (either from the originator company or from generic companies for older products) – which could be published and then adopted in terms of language and layout by all MA Holders. The approval could be published in a Pharmacovigilance “PAR”. Those MA Holders following the PAR version would then be exempt from doing further User Testing.

- 3) Use of Glossaries

Use of glossaries containing medical terms which are “translated” into language understandable and therefore accessible to a lay person should be prepared in each EU language. This should be initiated by Regulatory Authorities and could invite the input of Patient Groups, and organisations such as the “Picker Institute”, “Doctor Patient Partnership” and “Med Guides”. If the glossary is followed, there should be no need to User Test these medical terms.

- 4) Follow Leaflet format and language once User Testing has been passed

Also if a Package Leaflet has passed User Testing, and this is referred to in an EPAR or PAR, then other applicants should be able to follow the format and wording and cross-refer to the positive published User Test (by reference to the EPAR or PAR).

We are pleased to see that 4 (b) allows the possibility of using evidence on one User Test to other Package Leaflets in the same medicinal class. We suggest that ATC codes could be used as a basis for deciding the same medicinal class.

An example of ACE Inhibitors, plain

	C09AA ACE inhibitors, plain				
		DDD	Unit	Adm.route	Notes
C09AA01	Captopril	50	mg	O	
C09AA02	Enalapril	10	mg	O	
C09AA02	Enalapril	10	mg	P	
C09AA03	Lisinopril	10	mg	O	
C09AA04	Perindopril	4	mg	O	



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C09AA05	Ramipril	2.5	mg	O
C09AA06	Quinapril	15	mg	O
C09AA06	Quinapril	15	mg	P
C09AA07	Benazepril	7.5	mg	O
C09AA08	Cilazapril	2.5	mg	O
C09AA09	Fosinopril	15	mg	O
C09AA10	Trandolapril	2	mg	O
C09AA11	Spirapril	6	mg	O
C09AA12	Delapril	30	mg	O
C09AA13	Moexipril	15	mg	O
C09AA14	Temocapril	10	mg	O
C09AA15	Zofenopril	30	mg	O
C09AA16	Imidapril			

Table from <http://www.whocc.no/atcddd/>

The results of one user test for a representative of the group e.g. ramipril, could be used for all Package Leaflets for the same group, providing the same layout and language (how side-effects etc are expressed) are used.

The use of a Europe-wide approved glossary (see suggestion under 2.2 above) would lead to a harmonisation of phrases for medical terms, and remove the need to repeat user testing.

We are pleased to note that under point 5) that updating to the QRD of an already tested leaflet will not require retesting. This section should also state that updating to the QRD template should not be the trigger to require the User Testing of the leaflet for a medicinal product authorised before 30 October 2005. Also that in the Centralised Procedure, if the generic applicant follows the Original Product PIL (which has been User Tested) and also updates to the QRD template, this update of the tested-PIL will not require repeat User Testing (this point may be better covered in a Q and A document).

- 5) Europe follows initiatives already started

In the UK, the MHRA have already accepted the concept of a British Generics Manufacturers Association (UK Generic industry organisation) idea of sharing User Test reports, for different therapeutic groups (one User Test per therapeutic area). By sharing the reports, the generic companies will have the same layout as tested. It has been agreed that slight differences in SmPCs (which are inevitable from the different registration routes and timing) are not material to the Package Leaflet User Test, so it has been accepted in principle that cross-reference to User Testing results is valid where there are differences in the Package Leaflet texts.



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The EGA proposes that this initiative is rolled out and accepted across the EU, and would like to discuss this with the CMD(h) PIL WG at the earliest possible time.

All of these approaches need to be facilitated by agreement across Europe on Language of the Package Leaflet tested, and the cross recognition of User Test assessments.

Language for Package Leaflet used in the User Test

It is requested that the language used for the Package Leaflet tested can be in any EU official language, and the User Tests in English are acceptable for all national applications. Finland and France have previously requested User Tests in Finnish and French Package Leaflets respectively. There should be no obligation to conduct the User Test in the local language for national applications or MAs authorised before 30/10/2005. This would mean that for older products authorised by the national route, only one User Test would be required across Europe, and this would have the benefit of leading to the more rapid harmonisation of the Package Leaflet, irrespective of the Regulatory route of approval.

Cross Recognition of Approval by the Competent Authority

Approval by one Competent Authority should be accepted by other Authorities including for National MAs. In addition, it would be useful to have transparency on how Competent Authorities are assessing the results of User Tests, and some assurance that they are assessing to the same criteria. The time-lines for User Testing as such that Competent Authorities should give feedback to applicants more quickly, than current practice, particularly if retesting of the PIL is required. With the implementation of this provision, should come some latitude in assessment and give applicants the time to learn and improve from experience.

7. Annex 1

Recruiting participants

It is not clear why there is the suggestion that Leaflets for medicines to treat rare illnesses are tested among people who have or have had the illness. The test should be applicable to any suitable cross-section of the public, and a requirement that it is tested on actual patients or ex-patients means:

- a) This group may have specialist knowledge which may make the leaflet more accessible to them, whereas it should be understandable to a wider general population (including people just diagnosed taking the medicinal product for the first time, which is probably the most critical time for reading the package leaflet).
- b) it may be very difficult to recruit a suitable subset of people without access to confidential medical information and may possibly breach Data Protection legislation, also ethical approval may be required,



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- c) The pool of potential people to test a leaflet for a rare condition is likely to be small, and may be regional.

It is proposed this requirement is deleted, and that User Testing should be carried out on a suitable cross-section of the general public, this Leaflet may be piloted in a suitably informed patient group, who could provide their expertise and experience to improve the package leaflet ahead of User Testing

More guidance is required for dealing with testing in children who may or may not be responsible for taking their own medication. Any justified approach should be acceptable, although it needs to be appreciated that there may be social difficulties or hurdles in accessing children as a target population. Children may not have the maturity nor the attention span to participate effectively in the Package Leaflet User Test.



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Technical Annex on the Draft guideline on the readability of the label and the package leaflet of medicinal products for human use, revision September 2006

COMMENTS FROM EUROPEAN GENERICS MEDICINES ASSOCIATION

GENERAL COMMENTS

Additional comments are made here using the usual template for ease of navigation around a complicated guideline. It would be helpful in terms of navigation to have a consistent way of numbering and labelling the guideline and include a contents page and page numbering.

GUIDELINE SECTION Introduction

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Purpose Para 2	The purpose also should be to assist those carrying the assessment of Package Leaflets and Labelling. Reference to Specimens should be removed from the Guideline, testing and assessment is carried out on mock-ups of Package Leaflet and Labelling.	The guideline is written to assist applicants and marketing authorization holders when drawing up the labelling and package leaflets and preparing the "mock-ups" of the sales presentations, and also ensure the consistent application, interpretation and assessment across the European Regulatory Agencies.



Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Section A first para	Generic companies see a trend where Authorities increasingly ask for information to be included in the Package Leaflet which is only relevant to Healthcare Professionals e.g. detailed information about how a specific product may affect the results of a blood and urine test. Inclusion of unnecessary information, not aimed at the patient, can decrease the readability of the Package Leaflet, and this should be emphasised in the opening paragraph of the guidance.	Add the sentence in bold. A balance needs to be achieved between the length of the resulting leaflet and the accessibility of the information contained within it. It is emphasised that Marketing Authorisation Holders should only include information in the Package Leaflet which is relevant to the safe use of the medicine by the Patient. Information which is directed at Healthcare Professionals should be omitted.
Section A1 Line 2, Para 1	This section suggests that a serif typeface is preferred, however there is disagreement and many references on the comparative legibility of serif and sans-serif fonts. None of them is conclusive. The most legible typeface is the one which a person is most used to. It therefore depends on whether the subject reads books, newspapers, or just reading (e.g. newsbars) from the TV or from the Internet.	Delete the unnecessary sentences so that the Paragraph reads: Choose a font which is easy to read. Stylised fonts which are difficult to read should be avoided. It is important to choose, where appropriate, a typeface in which similar letters/numbers, such as "i", "l" and "1" can be easily distinguished from each other.
Section A1, Line 1, Para 2	The font size of the leaflet should be 12 point. Reference to a font size without a font type is meaningless. In most cases this will not be practical as the leaflets will be prohibitively large. The recommendation later in the guideline is that paper is A5 or A4 ! This is only feasible if there is agreement/suggestions on how to reduce the information in the leaflet. The headings in the QRD template add to the length of the Package Leaflet. Most companies use 7 and 8 point, and the Package Leaflets have	Include a minimum of font size e.g. 7, and a font reference (revert to the existing guidance section A 1).



<p>Section A2, Line 3, Para 2</p>	<p>passed User Testing. Most of the type read every day is 8 point. Provision of leaflets in large print is a requirement for those people with impaired sight.</p> <p>Spacing between lines should be at least 1.5 times the space between words on a line. In most cases this will not be practical as the leaflets will be prohibitively large.</p> <p>This section suggests the use of underlining which is inconsistent with Section A1 which states 'Do not use underlining'.</p>	<p>Spacing between lines should be at least 1.0 times the space between words on a line.</p>
<p>Section A3, Line 2, Para 1</p>	<p>It will be difficult not to use more than 5-6 bullet points particularly for side effects because lists of side effects are often considerably long.</p>	<p>This should be clarified by stating that underlining is acceptable for use in headings but not for the body of text</p> <p>Add guidance on how long lists of side effects should be presented and still meet the requirements of the readability guideline which recommends short paragraphs and short lists of bullet points.</p>
<p>Section A5, Line 3, Para 3</p>	<p>Giving reasons for every instruction will increase the length and wordiness of the leaflet and is inconsistent with Section 5 on Syntax where it suggests using simple words, short bullet points etc</p>	<p>It is not feasible to add a reason for every instruction, judgement by the MA Holder should be exercised when this is necessary, and whether it adds to the understanding of the Package Leaflet (may reference results from User Testing)</p>
<p>Section A6, Line 1 Para 2</p>	<p>Use of 'It' is not consistent with the QRD template where it states use of 'X' as the product name.</p>	<p>More guidance is necessary on the use of the product name and when it can be abbreviated to 'It' or an abbreviated product name e.g. Ondansetron vs Ondansetron 2mg/2ml Solution for Injection.</p>
<p>Section A6, Line 1, Para 3</p>	<p>Regarding translation of technical terms into language which patients can understand. A harmonised approach for lay terms and descriptions would be beneficial for the harmonisation of terminology across Member States.</p>	<p>Provide a list of standard lay terms and descriptions for use in leaflets.</p>



<p>Section A6, Line 1, Para 6</p>	<p>With respect to side effects, detail on the correct order to follow would support a harmonised approach in Europe. Currently there is disagreement between MS on the correct presentation of side effects e.g. frequency followed by seriousness or SOC followed by frequency. A standardized approach for the EU would aid harmonisation of labelling and a consistent approach across MS.</p>	<p>A standard recommendation for the order of side effects should be incorporated into the QRD template together with a list of lay terms and descriptions.</p>
<p>Section A7, Line 1, Para 1</p>	<p>In most cases the use of A4/A5 paper will lead to prohibitively large leaflets, particularly if the suggested font size of 12 is adhered to. For example, long leaflets packed in small cartons which need to include both a patient leaflet and a technical leaflet for the healthcare professional. We welcome the flexibility of the guideline to allow alternative sized leaflets when it is not practical for the manufacturers to use A4/A5 paper.</p> <p>The guidance should not be so prescriptive on the paper type used.</p>	<p>Paper A4/5 is preferable where practical.</p> <p>Glossy paper reflects light which may make the information more difficult to read, therefore manufacturers should consider using uncoated paper.</p>
<p>Section A9.2 Line 1, Para 1</p>	<p>The guidance mentions that information from the summary of product characteristics could be included instead of the entire SPC. This is contradictory to the QRD template which requests the inclusion of the entire SPC as a tear off portion.</p>	<p>The guidance should clarify what technical information would be required on the leaflet for healthcare professionals as an alternative to including the entire SPC. As space is limited, and healthcare professionals are busy people, it is suggested that an abridged form of the SPC is used with only information relating to the safe administration of the product is included (so the HCP does not have to read through a very long document). There should be no need to repeat information in the abbreviated SPC and Package Leaflet (e.g storage of the product is only applicable to the HCP).</p>



<p>Section A 9.2 para 2</p>	<p>Provision of Additional Package Leaflets.</p> <p>The Marketing Authorisation Holder fulfils its legal obligation by providing a User Leaflet (inside or information on the label) with each pack. This User Leaflet is added to the pack under GMP conditions and this ensures that the correct leaflet is contained within the packaging of the correct product. Supply of additional package leaflets would breach GMP. Hospitals need to reach their own way of ensuring that each patient receiving a medicinal product has access to the Package Leaflet, and have their own systems in place to make sure the correct Package Leaflet is supplied. It is impossible for the MA Holder to take measures to enable the hospital staff to provide the patient with the current version of the package leaflet. There will be regional variations in how this is achieved and this suggestion has no place in this guidance document</p> <p>There is no guidance on how to prepare Package Leaflets for products that are administered by healthcare professionals.</p>	<p>Delete 2nd paragraph of Section 9.2</p>
<p>Section A9.2 generally</p>	<p>Serious consideration should be given to exempt hospital-only products from User Testing - they are often very long and complicated, and in fulfilling the Regulatory requirements for what they need to contain make the information inaccessible. Some thought needs to be given to the situation in which patients are given the medication (e.g. cancer patients may receive several different medications at once) - discussion with suitable patient groups may help to discover what patients in a hospital setting really need to know - and supply this information in a suitable format. This could be in collaboration with organisations such as the Picker Institute, Doctor Patient Partnership or Med Guides.</p>	<p>It would be useful to include some guidance on the level of detail required for a product administered by a healthcare professional - details of the dose information are less important, and patients should be guided to speak to the doctor or nurse (not the pharmacist). The use of the leaflet is very different from the community and some further guidance on the content of a package leaflet for use in a hospital setting would be helpful.</p> <p>Alternatively, hospital only products could be exempt from User Testing, and explore other ways to get the message across to seriously ill people on poly-pharmacy (a more holistic approach to their illness and possible treatments).</p>



<p>Medicinal Product</p>	<p>reference the INN. The naming conventions across EU agencies is still an area where national conventions are applied” - being more precise in the guideline (i.e. keep in line with the wording of the Directive) may help national authorities become more consistent in their interpretation. Sometimes there is not enough room to accommodate the full name of the medicinal product, the guidance should include a pragmatic approach on this point.</p>	<p>(INN) shall be included, or if one does not exist, the common name. When there is not much space, it may not be possible to include the full pharmaceutical form, in a large enough font point size. Therefore some flexibility is allowed where there is not much space on the packaging or the full product name is very long. The use of the shortened term in the book of Standard Terms is acceptable under these circumstances, and justified by the applicant or MA Holder.</p>
<p>Section B3 Lines 4-5, Para 1</p>	<p>It is not clear under which circumstances routes of administration will need careful explanation to patients since the European standard terms for route of administration are used on the labelling.</p>	<p>Examples should be given.</p>
<p>Section C2 Small Containers Line 5, Para 1</p>	<p>A nominal capacity for small containers is given as 10ml or less. This does not cover all non solution formulations such as creams which are measured in grams.</p>	<p>We would welcome further guidance on the nominal capacity for small containers of products for which the contents are measured in units other than mls e.g. grams.</p>



GUIDELINE SECTION Chapter 3 Guidance concerning consultations with target patient groups for the Package Leaflet		
Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
3.1 User Testing Para 2	User Testing is carried out early in the development of products, and so User Testing is carried out on “mock-ups”. Also as Package Leaflets need revision and retesting, the only practical way to achieve this is to do the testing on mock-ups of the Package Leaflet	The first line of para 2 needs to be corrected to: User testing means to test the readability of a mock-up with a group of selected test subjects or other suitable method of testing.
4 Para 1	Starting the section with “In general” immediately allows an opportunity for inconsistency. It needs to be clear what events will trigger user testing. It is very unlikely that variation of a MA will require User Testing.	Suggest, rewording replacing the paragraph starting “In general”... “User Testing or other justified method for testing the readability of Package Leaflets is required before the grant of Marketing Authorisations, and form part of the Marketing Authorisation application. Other situations where a User Test is always required is given under (a) below”.
4 Para 2	This paragraph indicates that all Member States accept the QRD template, this is inconsistent with an earlier section of the guideline, which indicates that for national applications national templates may be used. This should be made consistent.	Leave para 2 as it stands, and amend the earlier paragraph as suggested above “The guidance needs to indicate that the QRD template should be followed for Mutual Recognition, Decentralised and Centralised applications, they should be used for National applications, unless the applicant has good reason to use an alternative National template. If the results of User Testing indicate that the QRD template needs to be changed, these changes should be allowed, and the Competent Authorities feedback, so that the QRD template can be updated and improved in the light to the results of User Testing”



<p>Section 6 1st para</p>	<p>The presentation of results in Module 1.3.4. is only possible if the User Testing is carried out ahead of the application. This needs to be rewritten to reflect the current Q & A documents so there is no conflict with other guidance. The application may also be made through other means, other than a new application, the guidance needs to accurately reflect this.</p>	<p>Reword Sentence 2. When the results of User Testing are submitted with an application for a Marketing Authorisation the summary should be in Module 1.3.4 of the application. The following structure is suggested for the results:</p>
<p>Section 6 final para</p>	<p>User test results should always be allowed in English - so that results of one User Test can be used for different national MAs, and lead to more consistency across Europe.</p>	<p>It is suggested that the wording is changed: The report and the results of the consultation should be presented in English for the centralized, decentralized, mutual recognition and national procedures. Applicants may alternatively choose to write the report in the national language for national procedures.</p>
<p>Section 8</p>	<p>There is currently much confusion and lack of harmony among Member States regarding the timing, submission and assessment of the User Testing - this guideline could be an opportunity to be much more transparent and make it clear to MA Holders exactly what will be required and when. The generic companies hold 10,000 of MAs across Europe and User Testing is a labour intensive, time-consuming and expensive exercise. It takes a lot of planning, and the ability to bridge and share User Test results across the industry will be essential to ensure that MA Holders can comply.</p>	<p>Guidance and agreement among Member States on timing, submission and assessment should be available now, and not be part of different or guidance to be developed.</p>



GUIDELINE SECTION TITLE ANNEX 1 Illustration - One Way of Undertaking a Test of a Package Leaflet		
Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Line 3, Para 2 Section 1 Line 1	<p>Where the paragraph states ‘...for whom the medicine is intended¹’, the superscript is not defined. Later the guidance states that you are allowed to recruit people ‘who are able to imagine needing to use the medicine’. The guidance appears to be contradictory. Clarification is needed regarding ‘population for whom the medicine is intended’ This should clearly refer to age groups/sex e.g. a Package Leaflet for a contraceptive tablet for female use only should be tested in female subjects aged 16 to 50.</p> <p>Bullet 1: suitably qualified company</p> <p>Bullet 4: The writer of the Package Leaflet (usually a Medical Writer or Regulatory Professional) is not necessarily the best person to carry out User Testing (they may not have interviewing skills required)</p>	<p>Include the description for the text for superscript. Make it clear that the target population are subjects who may take the medicine, and be consistent about this throughout the guideline.</p> <p>Suitably qualified company should be defined. With the introduction of User Testing, companies have started up opportunistically, or Regulatory Consultancies have offered this in their range of services. It is too early in the experience of User Testing to use the term “suitably qualified”, as there is no definition and standards. It is suggested this is changed to:</p> <ul style="list-style-type: none"> • Testing of Package Leaflets may be carried out by the MA Holder, or a company contracted by the MA Holder • Ideally the writer of the Package Leaflet will accompany the interviewer during User Testing.



<p>Section 2</p>	<p>Recruiting Participants</p> <p>Bullet point 2: there seems no reason to test people who have or have had the illness, the ideal is to test someone who potentially could have the illness (suitable sex and age range, see first point in this section). Besides this being more logical (the last people you should test are those who are knowledgeable already) - if the condition is rare, it will be difficult to recruit suitable numbers, it also poses ethical problems (would have to ask personal questions about medical condition) and is inconsistent with the idea of the “target patient population”.</p> <p>Inclusion of Young People (bullet point 4). More guidance is required on when User Testing on children is appropriate - it makes sense it is only done when the children are themselves for taking their own medication. There are social issues about adults spending time with children alone, so the guidance needs to specify that a parent or guardian or teacher is present.</p>	<p>Delete the bullet point which starts</p> <ul style="list-style-type: none"> • If the medicine is intended for a rare illness.... <p>Add to bullet point 4 Young people should only be user tested if they are responsible for taking their own medication e.g. using an inhaler at school. If the medicinal product is administered by an adult, e.g. antibiotic or paracetamol oral solution, the user testing should be carried out an adult (who is a parent/guardian/carer).</p>
<p>Section 3</p>	<p>Sample Size and Use - this heading does not make sense, the existing guidance is clearer, on how the User Test should be conducted. The section is very unclear and needs to be re-written (the suggested text here is written using the existing pass criteria (see point below on Section 4). There is no justification to tighten the pass criteria for this revision of the guidance.</p> <p>It needs to be clearer that minor revisions during rounds of testing do not require testing in two groups of 10 subjects, there needs to be some commonsense applied or otherwise the testing</p>	<p>Change the heading to “Suggested Testing Procedure”</p> <p>The aim is to meet the success criteria; that 16/20 consumers are able to answer each question correctly; it is not necessary for the same 16 people to answer each question correctly. The following approach is suggested:</p> <ul style="list-style-type: none"> o Conduct a pilot with 2-6 participants to see that the questions work in practice. Pilots may be with someone from the Target Population Group, or someone from suitable Patient Groups, or someone with appropriate experience (e.g. with formatting and how to express medical language in patient-friendly terms).



<p>Section 4</p>	<p>could be never-ending (particularly for complex User Leaflets e.g. those for oncology products) or where issues with the QRD template is raised.</p> <p>Success Criteria have been considerably tightened from the original guidance (the way it is expressed is different, but in essence has gone from 8/10 to 9/10). As the testing is still based on the Australian model of testing, the same success</p>	<ul style="list-style-type: none"> ○ Make revisions to the Questionnaire and Package Leaflet Mock-Up, if necessary, after the Pilot. ○ Conduct one round of testing in 10 people, and review results. If the same issue or question is problematic in 2 or more individuals and therefore there is a high chance that the Package Leaflet will not pass the User test, make further revisions to the Mock-Up ○ Once one round of testing is completed successfully in 10 people, proceed to test a separate group of 10 people. It is possible that due to random chance, that there is an uneven distribution of people, and issues may only come to light in the 2nd group of 10 subjects.. ○ The results of the two groups of 10 subjects are pooled, so testing (and revision of User Leaflet) needs to continue until the success criteria are met. If 30 subjects are tested, then the pass criteria is 24/30 subjects can answer each question correctly. If a very minor change to the User Leaflet is made/proposed - and the Package Leaflet passes in any case, repeat testing on the Final Version of the Package Leaflet in further groups of 10 subjects is not required. <p>The Previous Guidance Objectives and Testing point 8. should be reinstated under the heading Success Criteria</p> <ul style="list-style-type: none"> ● A satisfactory test outcome is to have at least 16 out of 20 consumers able to answer each question correctly. However it
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<p>Section 5, Last Para</p>	<p>criteria should be applied, as 20 years experience has shown is reasonable and achievable. The criteria should not be tightened, if at all, until there is more experience of User Testing. The objective should be SMART (Specific, Measurable, Achievable, Realistic and within a Time-frame)</p> <p>It is not clear from this last paragraph what documentation is required with the submission of the results of consultation with target patient groups to the Competent Authority. The last sentence says we need to include the interviewer's written observations. It is not clear whether this is meant to be the raw data collected by the interviewer or if a summary of the interviewer's written observations presented in the Summary Outcome Report is acceptable. According to Section 6. Presentation of the results, a summary and discussion of the results is acceptable.</p>	<p>is not necessary for the same 16 people to answer each question correctly. It may be necessary to modify the leaflet and then retest several times to achieve this level of performance.</p> <p>Clarification should be provided concerning the requirement for interviewer's written observations. The presentation, summary and discussion of results should be acceptable.</p>
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