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Draft Statement:
Guideline on the readability of the label and package leaflet of medicinal products for human use
(state of discussion: September 2006)

Via the Directive 2001/83/EC (1) as amended by Directive 2004/27/EC (2) several changes regarding the package insert design were published which concerned for example the new sequence of the arrangement and the accomplishment of readability tests. It is therefore absolutely necessary to adapt the ”Guideline on the readability of the label and package leaflet of medicinal products for human use” (3), which has for many years already existed, not only to coincide with the new legal requirements, but also new scientific findings and practical experiences.

Above all, the practical implementation of new requirements raised questions relating to the conversion consistency. Therefore, based on the experiences of PAINT-Consult as provider of user tests in addition to package insert research for over seven years, a statement is delivered to the draft specified above in the following. According to PAINT-Consult’s thematic focus, as well as recommendations to develop package inserts, the necessity to implement new required user tests should also be mentioned.

Putting new recommendations in place for discussion, before implementation, is in principle positive as it facilitates the inclusion of useful suggestions from practical experiences. The perception of the European Commission contained in the draft is of special interest, as questions frequently asked concerning the development of package inserts and the implementation of user tests are addressed and/or answered therein.

Chapter 1 Readability of the Label and the Package Leaflet

Section A The Package Leaflet

1. Print size and type

Above all, the readability is consistently an important point of criticism in package inserts (4, 5, 6). Small writing in particular, is a cause of major problems (6, 7). In addition to the font size, typeface and colour of the type, line space and background are also important (8, 9).
In relation to this, choosing a font which is easy to read, is recommended in the first point. Thus, a clear distinction between letters, numbers and other punctuation marks is possible. In addition, for reasons mentioned above, the guideline should include that the typeface should not contain decorations on the letters or numbers.
The specific definition of the typeface is positive, and can be applied more precisely. However, in the example presented, the number “1” cannot be distinguished from the lower case letter “l”. According to the criteria mentioned before, this is evaluated as less appropriate.

Although semi-bold serif typefaces are more frequently used in some countries, excellent readable typefaces exist which have no alphabetical or numerical decoration. It must be ensured, that typefaces such as these can also be used in the future.
In point 2 under the heading „Print size and type“, a general font size of 12 pts is recommended. It must be stated that this recommendation is unrealistic and rarely applicable, owing to the constant increase in text extent.
An 11 pt font size is recommended for package inserts, to target optimal reading, as this size is fastest to read (7, 10). According to Bernardini et al. and Boyce a 10 or 12 pt font size is only slightly inferior compared to an 11 pt font. Font sizes beginning at 14 pts can even have a negative affect on the reading rate, as the reader recognizes the words more slowly, compared to smaller written texts (10). For this reason a general font size larger than 13 pts should not be recommended or realized, even if the target groups of the appropriate medicinal product are more often patients with visual impairment.

Using font sizes from 16 to 20 pts would cause the package insert format to become particularly difficult to manage and patients without visual impairments may be surprised by the large font. In addition the readability would be impaired and reduced for these patients according to the arguments specified above.
To meet the needs of people with visual impairments, each cardiovascular or anti-diabetes package insert would have to be designed using larger font sizes, as elderly people are

generally known to need these medicinal products and suffer more frequently from visual impairment.

A more appropriate font size of 10 or better still, 11 pts should be recommended in the main text. These are more realistic conversions, compared to the existing draft, and guarantee optimal readability. Larger font sizes should be rejected.
Furthermore, recommendations that are unattainable are not suitable for a European guideline, as only very few companies would be able to implement them.

The headings should be written at least 2 pts larger than the main text. According to the PAINT1-study and the realization of the previously mentioned recommendation, an optimal locatability and readability of package inserts can be achieved (6) (PAINT - **pa**ckage **in**sert **t**est, a Cross-Over-Comprehensibility-Test of original and model package inserts with 1105 participants - see appendix).

As the third point correctly specified, words written only in capitals are not recommended. Using this notation, differences in letter heights are not easily recognized, for example the letter “g”, compared to the usual notation with upper and lower case letters.
Various reading tests have illustrated that, words written only in capitals are read slower than words written with upper and lower case letters (10, 11, 12).
This is similar with underlined words. Outline differences of the lower surface are noticed with more difficultly.

Examples:

Package leaflet PACKAGE LEAFLET <u>Package leaflet</u>

Bold print, different font colours, and/or different font sizes are significantly more suitable for emphasizing certain words, even when it concerns only a small text. On account of this, using capitals for emphasis cannot be recommended. This suggestion should therefore be removed.

2. Design and layout of the information

The recommendations contained in this chapter are widely applicable in improving the readability of package inserts. However, while 1.5 times space between one line and the next enhance reading, it is rarely convertible since the texts are often extensive.

The landscape format recommended in the fourth point should be eliminated, since this format can cause an increase in column changes within one chapter. In addition, there is no clear proof that landscape format is better than portrait format.

3. Headings

According to the contents of the first point, only bold print, different font colours and/or font sizes should be recommended to emphasize headings.

The recommendation regarding underlining must be removed, mainly because a sufficient number of more applicable methods exist and also due to the reasons already specified above.

4. Print colour

The recommendations specified here are also embraced by PAINT-Consult, as these conversions ensure good readability.

5. Syntax

The recommendation to use short sentences with a maximum of 20 words is particularly welcome as this issue only rarely receives attention e.g. in German package inserts, even though it has been stated in the guideline since 1998 (13).

The fact that this recommendation which has existed for 8 years, is not consistently considered, even in some QRD-Template sentences (3, 14), must be criticized. Pharmaceutical companies are therefore unable to completely apply the „Guideline on the readability of the label and package leaflet of medicinal products for human use" for formal reasons. For example, the following sentence found in the QRD-Templates under the subheading „Taking other medicines" could be significantly more condensed. The non quantifiable phrasing "recently" (4) should be defined more precisely corresponding to the specified interactions.

QRD-Template:

„Please tell your <doctor> <or> <pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription." (14)

With regard to the fourth point, as alternative appropriate numeration phrasings exist, switching the word “should” with the word “could” presents more possibilities.
The sentence which states, “No more than five or six bullet points in a list are recommended”, should be excluded, as information given in more than six bullet points is much clearer is some cases, compared to six elongated points.

6. Style

Recommending an active style in this draft guideline, can been seen as positive. However, this kind of patient motivation must be used carefully, e.g. in headings or contents of particular importance only. When this medium is used too frequently, the reader will no longer notice it as the effect is minimised.

According to this draft, repetitions and abbreviations must be avoided. However, they have to be used in the QRD-Templates (14), this leaves pharmaceutical companies with no chance of completely fulfilling this guideline.
For example consulting a doctor or pharmacist as an action when side effects occur is recommended by the QRD-Templates in the information box (below the name of the medicine) and under the heading “Possible side effects” (14).

The recent specification of the Marketing Authorisation Holder’s European selling countries and the medicinal trade names in the QRD-Templates include the abbreviation "EEA". This abbreviation is generally not well-known to patients. Examples of this ambiguous interpretation are as follows:

- **European Environment Agency;** under: www.eea.europa.eu/
- **European Energy Award;** under: http://www.eea.nrw.de/
- **European Economic Association;** under: http://ec.europa.eu/comm/external_relations/eea/index.htm
- **Einheitliche Europäische Akte;** under: http://de.wikipedia.org/wiki/EEA

In addition to the abbreviation „EEA“ pharmaceutical companies have other abbreviations, such as the inactive substances E-numbers and their dispensatory related to the ingredient substances such as, "Ph. Eur.".
Both are generally not comprehensible for patients. Substances with E-numbers are frequently classified by consumers as dangerous, even if they concern harmless substances such as saccharose.

Therefore, it must be ensured that as a result of the possible consistent implementation of this directive, pharmaceutical companies are not compelled to include the abbreviations mentioned in package inserts as these abbreviations are inappropriate for patients.
Further abbreviations like i.v., i.m. and s.c. are accepted in section B of this guideline under the heading „3. Route of administration“. These abbreviations should not be recommended since they are not generally comprehensible, especially for non-professionals. Complete words are significantly more suitable and should be recommended.

The last section in point six „Style”, recommends not specifying sub-headings and giving an appropriate reference where no information is known. This view cannot generally be appreciated.
For example, if no interactions are known for a medicine this should be appropriately listed under the heading „Taking other medicines“. Otherwise, patients may believe that important information is being withheld from them. In addition, this statement is helpful even in case of no interaction, as it enhances the patients confidence in the medicine.

7. Paper

An A5/A4 paper format is recommended for large package inserts and a more condensed text extent is generally desired in all package inserts (15). However, in the near future shorter package inserts will not be possible.
If the format A5/A4 is used for extensive package inserts, page changes within chapters could more frequently occur. It is well known that these reduce the possibility to locate and comprehend the information (6, 16). This is certainly not the intention, therefore under momentary conditions, paper formats larger than A4 are more suitable for some package inserts and should be accepted.

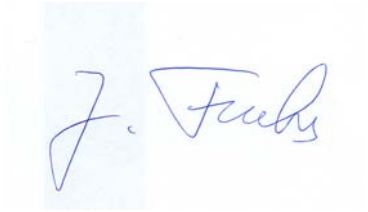
Annex 1 Illustration – One way of undertaking a test of a package leaflet

In general, it is also good to give examples for implementation of readability tests. However, the draft only mentions the test via interview in this context, which gives the impression that this is the best test procedure. This is not really proven.
It is known that a multiplicity of further tests already successfully accomplished, exist in the European Union. At this point the principle of equal rights must be protected, particularly as test procedures may exist which may be even better than the interview.
The fact that data relating to the location of the user test interview, is missing, must be criticized. This is important, as the package insert should be tested in a normal environment. A separate area, in which participants are shielded from outside disturbances, must be considered as less appropriate, as this situation occurs rarely in the patients’ everyday life.

The specified criteria for success must also be evaluated critically: 90% of participants are supposed to find all of the required information, thus, 90% have to understand the information located.
5% of adults in Germany have significant reading and writing difficulties (17). This fraction is substantially even larger in other European Union countries. According to chapter 2 “Recruiting participants“, participants who use little literature and/or have problems with written texts, should also be included in the test. However, in this case even with very clear and well comprehensible package inserts it is not always possible to achieve Sless and Wisemans’ recommendations (18) in an honest way, given that the test should be taken under everyday life conditions.

Bearing in mind the reasons mentioned previously and/or fluctuations in the participants’ or interviewers’ state of mind, the following success criterion is more realistic:
80% of the participants have to find and understand all required information in the total result.

Considering this standard, the minimum success ratio of the total result of 81% of located and comprehended information would be met, according to the draft (90% located, thereof 90% comprehended results in 81% located and comprehended information). Simultaneously, due to the small number of participants it is considered, that among the participants, 2 persons can be found who generally have large difficulties in reading and comprehending texts.



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Appendix: PAINT1-study, a Cross-Over-Comprehensibility-Test of 5 original and 5 model package inserts [abstract] (2)

[Fuchs, J.; Hippius, M.; Schaefer, M.: Package inserts and their comprehensibility for patients. Proceedings Workshop Programme and Abstracts - 13th international social pharmacy workshop (2004) 42.]

Package inserts and their comprehensibility for patients

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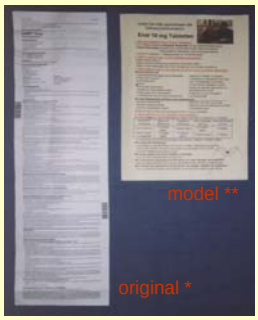
Background:
• Package inserts are very important for patient information
• Their suitability is still under discussion.
• Recommendations for testing the readability are given by the European Commission. [2]
• According to Sless and Wiseman: [1]
1. Over 90 % of the patients find the relevant information.
2. Over 90 % of those finding the information are able to understand it.
3. Thus over 81 % of the patients in total are able to use the package inserts appropriately.

Aims:
• The PAINT survey (package insert test) examined the comprehensibility and availability of information from five package inserts * for different drugs and five model package inserts ** for the same drugs developed for this test.

Methods:
• A questionnaire with 15 questions referring to the content of the package inserts was adapted using references by Sless and Wiseman [1], the EMEA [2] and the EFPIA [3] for a written survey.
• 1,150 patients were asked to participate in the PAINT survey.
• Cross over testing
• Every person got an original * and one model ** package insert within an interval of 4 weeks.
• Time: September 2002 to April 2003



Results:
• 1,105 persons answered the questionnaire in the first trial and 1,051 in the second trial (return rate: 95.9 and 91.2 %).
• Participants:
- 10 to 92 years old, average age: 38 years
- 69.1 % living in or near Jena, 30.9% in other parts of Germany
- 65.4 % woman, 34.6 % man
• Questions to the content of package inserts (Table 1)
- original versions: 74.7 to 85.8 % of all questions were answered correctly
3.8 to 6.9 % answers not found
- model versions: 92.6 to 94.4 % of all questions were answered correctly
2.2 to 2.5 % answers not found
• Time needed to answer the 15 questions (Table 2)
- original versions: 14.3 to 19.6 minutes
- model versions: 10.9 to 13.8 minutes
• The question: „What is the maximum dose for a day?“ (Table 3)
- original versions: 9.4 to 90.2 % answered correctly
0.9 to 9.9 % answers not found
- model versions: 83.6 to 94.0 % answered correctly
0 to 0.5 % answers not found
Frequently mistakes regarding the original package inserts were connected with dosage instructions in milligram instead of „tablet“ or volume. The maximal daily dosage was better found in those versions presenting this information in a table.

Conclusions:
• It is possible to improve package inserts.
• All models but only 2 original package inserts are easy to understand.
• With regard to dosage instructions the following is recommended:
1. Every dose should be given in a number of tablets or capsules and volume respectively.
2. Dosage instructions should be given in a table.

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PAINT
Package Insert Test

Table 1: Correctness of answers concerning the content of original vs model package inserts (15 questions)

package insert	correct answers (%) (calculated median)		answers not found (%) (calculated median)		n	
	original	model	original	model	original	model
Enalapril	78.5*	93.2	6.7*	2.5	218	214
Ibuprofen	85.8*	94.4	6.9*	2.3	215	213
Paracetamol	82.6*	93.3	3.8*	2.2	213	219
Repaglinide	79.0*	93.3	4.5*	2.3	214	216
Telmisartan	74.7*	92.6	6.2*	2.3	213	216

(* significant differences between the results of the original and the model version of package inserts)

Table 2: Calculated median of the time needed to answer the 15 questions

package insert	time to answer the 15 questions (min)		n	
	original	model	original	model
Enalapril	19.6*	13.1	203	197
Ibuprofen	18.8*	12.4	200	200
Paracetamol	14.3*	12.0	197	203
Repaglinide	15.3*	13.8	204	199
Telmisartan	15.3*	10.9	195	198

(* significant differences between the results of the original and the model version of package inserts)

Table 3: Calculated median for the answers to the question: “What is the maximum dose for one day?”

package insert	correct answers (%)		answers not found (%)		n	
	original	model	original	model	original	model
Enalapril	52.5*	83.6	0.9	0	217	213
Ibuprofen	90.2	90.0	1.4	0	215	210
Paracetamol	9.4*	84.9	7.0*	0	213	218
Repaglinide	36.0*	94.0	7.5*	0.5	214	216
Telmisartan	33.3*	92.1	9.9*	0.5	213	216

(* significant differences between the results of the original and the model version of package inserts)