Readability of the European QRD Template

The European QRD template version 8 in comparison to its predecessor and a shorter model template

Anna Wolf[1], Jörg Fuchs[1,2], Harald G. Schweim[1]

[1]Department of Drug Regulatory Affairs at the Institute of Pharmacy, University of Bonn, Bonn, Germany
[2] PAINT-Consult®, Jena, Germany

Correspondence: Dr. Jörg Fuchs, PAINT-Consult®, Wenigenjenaer Ufer 12, 07749 Jena, Germany; e-mail: joerg.fuchs@paint-consult.com

ABSTRACT

Package leaflets of medicines distributed within the European Union must use the QRD template headings and standard texts; however, research on this important text frame is very rare. In the following study the QRD template versions 8, 7.3.1 and a shorter model template were investigated. Package leaflets with these three templates were created using three enalapril texts: the German BfArM sample text, and a condensed German version of the BfArM sample text and its English translation. The text condensation reduced the number of words without deleting information essential for patients. Using the written readability test, every participant tested one enalapril leaflet text only, but all three templates, with a 6 month time gap. For the condensed leaflet text, 75 German participants provided 93.2 %, and 67 English participants 95.0 % provided correct answers to 26 content questions when using the model template compared to QRD template 8 (91.1 and 91.5 %) and 7.3.1 (87.3 and 83.4 %) ($p \leq 0.026$). For the long BfArM sample text, 94 other German participants provided similar correct answer levels with QRD template 8 (81.2 %) and the model template (80.4 %), however, significantly more compared to QRD template 7.3.1 (76.2 %, $p \leq 0.001$).
In addition to the identified QRD template improvements of version 8, optimisation is still possible. Condensation of the QRD template text should be seriously considered as the shorter model template showed significant advantages over both investigated QRD templates.

KEY WORDS

- Model template
- Package insert
- Package leaflet
- QRD template
- Readability test

ZUSAMMENFASSUNG

Die Lesbarkeit des europäischen QRD-Templates / Das europäische QRD-Template Version 8 im Vergleich zur Vorgängerversion und einem kürzeren Modelltemplate

Packungsbeilagen von innerhalb der Europäischen Union vertriebenen Arzneimitteln müssen die Überschriften und Standardtexte des QRD-Templates enthalten. Jedoch sind Untersuchungen dieses bedeutenden Textgrundgerüstes kaum vorhanden. Die nachfolgende Studie untersuchte die QRD-Templateversionen 8 und 7.3.1 sowie ein kürzeres Modelltemplate. Enalapril-Packungsbeilagen wurden mit diesen drei Templates erstellt auf Basis des deutschen BfArM-Mustertextes, sowie mit einer komprimierten deutschen und englischen Version dieses Mustertextes. Die Textkomprimierung beinhaltete eine Verringerung der Wortanzahl ohne Entfernung von essentiellen Patienteninformationen. Unter Einsatz des schriftlichen Lesbarkeitstestes testete jeder Studienteilnehmer nur einen Enalapril-Packungsbeilagentext, aber mit allen drei Templateversionen im Abstand von 6 Monaten. Bei den komprimierten Packungsbeilagen beantworteten die 75 deutschen Teilnehmer zu 93,2 % und die 67 englischen Teilnehmer zu 95,0 % die 26 Inhaltsfragen richtig, wenn das Modelltemplate verwendet wurde, verglichen mit dem QRD-Template 8 (91,1 bzw. 91,5 %) und 7.3.1 (87,3 bzw. 83,4 %) ($p \leq 0.026$). Beim langen BfArM-Mustertext lieferten 94 weitere deutsche Teilnehmer ähnliche Quoten richtiger Antworten beim QRD-Template 8 (81.2 %) und Modelltemplate (80.4 %), jedoch signifikant höhere im Vergleich zum QRD-Template 7.3.1 (76.2 %, $p \leq 0.001$).
Trotz den gefundenen QRD-Templateverbesserungen der Version 8 sind weitere Optimierungen möglich. In diesem Zusammenhang sollte eine Textverringerung des QRD-Templates unbedingt berücksichtigt werden, da das kürzere Modelltemplate signifikante Vorteile gegenüber beiden untersuchten QRD-Templates zeigte.

Pharm. Ind. 76, No. 8, 1–10 (2014)

1. Introduction

Package leaflets are important patient information and must be provided with all medicines distributed within the European Union (EU) [1–3]. To harmonise the order of information, headings and standard texts of package leaflets, the European Medicines Agency's (EMA) Working Group on the Quality Review of Documents (QRD group) created the so called QRD template [4]. During development of QRD template version 8 (for centralised approved medicines) and version 2 (for other medicines) in 2011, headings and mandatory texts underwent major changes based on information gained from user testing and feedback from various sources. The concerned user testing results are a collection of problems identified from QRD template version 7.3.1, although the methods and resulting data used to create these amendments remain unpublished [5]. The most recent QRD template versions 9 and 3, respectively, from spring 2013 provided two text additions as a result of the latest pharmacovigilance legislation [6–8]. Despite the major influence on all medicines' package leaflets distributed in the European Union, relevant studies with the updated QRD templates have not been carried out. Moreover, since the first QRD template published in 1996 the number of words intended for each leaflet has expanded from less than 100 to over 800, with the long list of company representative addresses not yet being considered in this total [9]. Increasing package leaflet's text volume has been shown to decrease the locatability of information, motivation to read the leaflet and confidence in the medicine [10, 11]. The negative effects of the increased text volume have not been addressed in the QRD template although previous studies have shown the advantages of a significantly shorter model template of around 200 words – mainly through avoiding repetitions and long sentences [11, 12].

The study described in this article addresses the problem of insufficient data and compares QRD template 8 to its predecessor and the short model template using two languages.

2. Materials and methods

Three package leaflet groups each with the three different templates were developed using QRD template version 7.3.1 (personal communication, EMA) and 8 [5], and a model template with less than 200 words which had been tested in a previous study [11]. The latter is named in the following as "model template". The QRD template 8 for centralised procedures was chosen as it had been updated at the time the study started. The maximum template text was used according to the QRD template bracketing convention. Therefore, leaflets with QRD template 7.3.1 or 8 contained an address list of 29 country representatives of the marketing authorisation holder as recommended in these templates.

The BfArM (Federal Institute for Drugs and Medical Devices, Germany) sample text for the prescription only ACE-inhibitor enalapril tablets was selected to develop a company independent leaflet, even though this substance is not approved by the centralised procedure [13]. Versions of the leaflet were created which contained the full length text provided by BfArM using the three templates. This text was then condensed and optimised to contain identical information but as a series of concise bullet points in the same templates to provide an easily readable comprehensive text comparable to similar enalapril package leaflet texts tested in previous studies [11, 12]. As a result, three groups of package leaflets – the condensed text version in German and English and the long BfArM sample text in German – were tested with each of the three templates. All leaflets were printed with an identical layout and design to ensure standardised conditions. (See *http://paint-consult.com/eng/publikation/pdf/QRDtemplatestudyleaflets.pdf*).

Readability testing has been the current EU gold standard to assess package leaflets since the implementation of Directive 2004/27/EC [14]. This study used the written readability test, also named 'self-completion' method [15] as this was developed to compare package leaflets and ensures identical test conditions independent of the leaflet or language used [12].

A cross-over study design was used whereby each subject had to test all three template versions of one of the three leaflets groups with a minimum 6 month time interval between testing each template version as recommended [16]. To obtain reliable data, over 60 participants per package leaflet group were involved. Participants with a broad range of literacy and age were recruited randomly as long as they were able to independently read the leaflet and answer the questionnaire. The identical questionnaire used in each of the three test rounds started with a cover letter followed by sections for demographic data and 26 questions for testing template key messages. Participants were asked to note the times when they started answering the 26 questions and then again when they had finished. The time taken to answer each individual question was not measured according to the written readability test procedure [15]. The questionnaire also contained 15 statements for participants' opinions on the leaflet using a 5 point Likert assessment scale. In a free text section, participants could describe what they liked/disliked about the tested leaflet or what should be included or deleted.

A questionnaire test was performed with 4 participants per prepared leaflet before study begin.

The answers provided in the questionnaires were coded and entered into a SPSS 15.0 table using double data entry. The following categories were used for rendition of package leaflet content questions: 'correct answer', 'wrong answer' and 'not found answer'. To minimise negative influences of outliers, the calculated medians of the total percentages correct, incorrect and not found answers to the 26 content questions and the time needed to locate and provide the requested information were determined using the SPSS statistics program. Percentages of correct, incorrect and not found answers were also calculated for each content question per leaflet.

Statistical differences between the three template versions' total correct, wrong and not found answers and locatability time per leaflet group were calculated using the Wilcoxon test in the program SPSS [17]. Differences between the results for each single content question were calculated using the chi-square test as a global test followed by the test after McNemar. Subsequently the Holm-alpha correction method was used [18].

3. Results

In total 241 people, predominantly from the Lichtenfels and Bamberg areas (Germany) and Cambridge area (United Kingdom) participated in the study between January 2012 and March 2013. With the exception of one participant in England, all participants were native speakers of the main

Pharm. Ind. 76, Nr. 8, 1312–1322 (2014)

Table 1

Demographic data of participants.*

Aspect	England Condensed package leaflet	Germany Condensed package leaflet	Germany BfArM sample text package leaflet
No. participants	69	76	96
Age range (years)	24 – 79	16 – 78	14 – 79
Average age (years)	52	42.2	36.4
Gender of participants	64.7 % female 35.3 % male	57.9 % female 42.1 % male	61.5 % female 38.5 % male
Participants who took no medication (%)	38.2 %	65.8 %	59.4 %
Level of education			
8th class	0 %	9.2 %	43.8 %
10th class	7.2 %	35.5 %	12.5 %
A-level	10.1 %	11.8 %	10.4 %
Polytechnic	7.2 %	5.3 %	8.3 %
University	66.7 %	14.5 %	18.8 %
Other	8.7 %	23.7 %	6.3 %

* At the start of the study itemised for the three investigated package leaflet texts.

language spoken in their countries. The demographic data of the participants is shown in Table 1.

With 95.0 and 93.2 %, the highest percentages of correct answers for the condensed text versions in each country were provided by participants who had read leaflets with the model template, followed by QRD template 8 (Table 2). Significant differences were found for the number of correct answers provided between the three templates per leaflet group ($p \leq 0.026$) except for the long BfArM sample text versions between the model template and QRD template 8. Significant differences were also found between all leaflet versions for the number of wrong answers provided with the best comprehensibility always being when using the model template ($p \leq 0.001$). In Germany, participants stated significantly more not found answers with the model template in comparison with QRD template version 7.3.1 for the condensed leaflet ($p = 0.006$) and for the long BfArM sample text version between the model template and both QRD templates ($p \leq 0.001$). The most frequent problems with locatability and comprehensibility arose from information regarding contraindications, precautions and possible side effects.

Participants required the longest time when using leaflets with QRD template 7.3.1 and mostly the shortest in the case of the model template (Table 2). However, a significant advantage for the model template in the locatability time was only found for the long BfArM sample text in comparison to QRD template 7.3.1 ($p = 0.008$) and QRD template 8 ($p = 0.003$). Layout and design of each leaflet were identical and therefore could not influence the length of time needed to find information or comprehensibility. The number of words was also identical in each leaflet version with exception of the different template volume of text, and that nearly 450 words in the leaflets with QRD templates 7.3.1 and 8 arose from the list of 29 country representative addresses of the marketing authorisation holder.

The question "Can you take this medicine if you are allergic to lactose?" showed the fewest correct answers in the study (Table 3). Significant advantages of the model template in comparison to the QRD template version 8 were found for the number of correct answers provided in England ($p = 0.015$). In general, this tested information was usually misunderstood for leaflets with QRD template 7.3.1 or 8 and 'not found' for leaflets with the model template. The model template package inserts only listed lactose in the excipients list at the end of the leaflet whereas QRD template versions 7.3.1 and 8 contained an additional subheading at the end of section 2 that the product contains lactose and the warning as stipulated by the Excipients Guideline, which was mostly the cause of the comprehensibility problems [19].

When information was requested contained in package leaflet section 2 under the sub-heading "Take special care with X" / "Warnings and precautions", the lowest percent of correct answers were provided by participants in England who had read the leaflet with QRD template 7.3.1. Participants were asked how they should act if they have to undergo a dental operation. The most correct answers were provided by participants using the model template independent of language and the length of the leaflet texts (Table 3). Significant differences in correct answers provided were found between each template version in Eng-

Table 2

Calculated medians relating to all 26 package leaflet content questions.*

Package leaflet	No. of words per package leaflet	Calculated median				n
		Correct answers (%)	Wrong answers (%)	Not found answers (%)	Time to answer the 26 content questions (min)	
English-Model-template-condensed text	1221	95.0	1.3	3.6	17.8	67
English-QRD-template-7.3.1-condensed text	2169	83.4	11.6	3.4	19.7	65
English-QRD-template-8-condensed text	2227	91.5	5.2	3.0	19.3	65
German-Model-template-condensed text	1007	93.2	2.2	4.4	20.7	75
German-QRD-template-7.3.1-condensed text	2002	87.3	9.7	2.7	23.4	72
German-QRD-template-8-condensed text	2023	91.1	5.0	3.3	20.3	73
German-Model-template-BfArM text	2893	80.4	7.7	11.1	24.5	93
German-QRD-template-7.3.1-BfArM text	3890	76.2	15	7.6	29.2	93
German-QRD-template-8-BfArM text	3956	81.2	11.5	6.5	28.6	94

* Percentages of correct, wrong and not found answers per package leaflet and the time needed to answer the 26 questions relating to package leaflet content.

land and in Germany between condensed package leaflets with QRD template 7.3.1 and 8, as well as model template and QRD template 7.3.1 ($p \leq 0.002$). The most common incorrect answer given for package leaflets with QRD template 7.3.1 was that 'special care' should be taken without providing a specific action if a dental operation is required.

Side effects were contained in section 4 of each leaflet, although the presentation of the frequencies and the wording used differed between each template version. For example, the "rare" side effect frequency:

- QRD template 7.3.1: "less than 1 in 1000, but more than 1 in 10000 patients" (using a table with frequencies at the beginning of section 4)
- QRD template 8: "may affect up to 1 in 1000 people"
- model template: "affects 1 to 10 per 10000 people"

(QRD template 8 and the model template both provided frequency explanations as subheadings).

Over 90 % of the participants stated the correct numeric frequency for 'How many people are affected by a side effect if it is "rare"?' regardless of the description method used (Table 4). However, the subanalysis of the answers showed that especially the wording recommended since publication of QRD template 8 led to overestimations of side effects' frequencies (Table 4).

In addition, participants were asked to which frequency group a side effect belonged if it affected 5 in 100 people. Similar to the subanalysis findings of the previous question, significant differences in the number of correct answers existed between all template versions. An advantage for the frequency explanations of the model template was identified ($p \leq 0.031$). QRD template 8 readers' problems were mostly the categorisation as "uncommon" frequency instead of "common" (Table 5).

The wording at the end of section 4 regarding how to act when side effects occur differed between each template version. Patients were asked how to act if they noticed the side effect "runny nose". Here, the QRD template version 8 wording showed the best results (Table 4). There was a significant difference between the number of correct answers for the long BfArM sample text between the model template and QRD template 8 ($p = 0.009$). In England there were significant differences in the number of correct answers between each of the three templates investigated ($p \leq 0.012$). Again, layout and design influences on these results, such as column breaks or salient heading can be excluded as no differences existed between the tested templates.

To condense the text volume of the template, the model template package leaflets contained neither information box nor contents list at the start of the leaflet in contrast to both QRD templates. However, information concerning the prescription status – content of the QRD template information box – was mentioned in the storage section of model template leaflets. The question relating

Pharm. Ind. 76, Nr. 8, 1312–1322 (2014)

Table 3

Questions relating contraindications, warnings/precautions and further information.*

Package leaflet	Average (%)												n
	Can you take this medicine if you are allergic to lactose? (contraindication question)			What should you do if you need a dental operation while taking Enal? (warnings/precautions question)			Is this medicine available with or without prescription by a doctor?			Name the active substance in Enal.			
	Correct answers	Wrong answers	Not found answers	Correct answers	Wrong answers	Not found answers	Correct answers	Wrong answers	Not found answers	Correct answers	Wrong answers	Not found answers	
English-Model-template-condensed text	41.8	10.4	47.8	91.0	0	9.0	80.6	1.5	17.9	100	0	0	67
English-QRD-template-7.3.1-condensed text	33.8	60.0	6.2	12.3	70.8	16.9	87.7	1.5	10.8	100	0	0	65
English-QRD-template-8-condensed text	20.0	75.4	4.6	72.3	0	27.7	87.7	4.6	7.7	98.5	0	1.5	65
German-Model-template-condensed text	38.7	20.0	41.3	97.3	1.3	1.3	65.3	1.3	33.3	92.0	1.3	6.7	75
German-QRD-template-7.3.1-condensed text	29.2	61.1	9.7	48.6	40.3	11.1	80.6	5.6	13.9	95.8	1.4	2.8	72
German-QRD-template-8-condensed text	30.1	68.5	1.4	89.0	2.7	8.2	76.7	4.1	19.2	98.6	0	1.4	73
German-Model-template-BfArM text	35.5	20.4	44.1	88.2	1.1	10.8	79.6	1.1	19.4	78.5	14.0	7.5	93
German-QRD-template-7.3.1-BfArM text	36.6	50.5	12.9	80.6	3.2	16.1	82.8	5.4	11.8	75.3	23.7	1.1	93
German-QRD-template-8-BfArM text	37.2	57.4	5.3	81.9	2.1	16.0	83.0	3.2	13.8	81.9	12.8	5.3	94

* Percentages of correct, wrong and not found answers for each package leaflet for questions relating contraindications, warnings/precautions and further information.

to this information was answered significantly more often with 'not found answer' by participants using the condensed German model template package leaflet in comparison to both QRD templates ($p \leq 0.035$). Significant differences in the percentages of correct answers were not found between the three template versions (Table 3).

Information on pregnancy and breast-feeding was provided in model template leaflets in the special warnings or contraindications sections only. The percentages of correct answers to two questions relating either to use during pregnancy or breast-feeding showed no significant advantage of any template version independent of whether this information was repeated in a separate QRD template paragraph or not (correct answers: ≥ 87.1 %, except 76.3 % for QRD template 7.3.1 and BfArM sample text).

A further question asked participants to name the active substance, which was provided in model template leaflets only in section 6, but additionally in all QRD template leaflets under the medicine name at the beginning of the leaflets and in QRD template 8 versions for a third time in the indication chapter. With 75.3 to 100 % correct answers for all leaflet versions, significant differences between the templates were not found (Table 3).

The participants' opinions on the structure of all package leaflets read were mostly positive and confidence in the medicine was neutral. The subheadings in QRD template 8 were significantly more positively evaluated than those in QRD template 7.3.1 for the BfArM sample text package leaflets ($p = 0.010$). In terms of whether the content of the package leaflet was difficult to understand, leaflets with QRD template 7.3.1 were rated significantly worse than

Table 4

Answers to the question: How many people are affected by a side-effect if it is rare?

Participants' description of frequency	Participants (%)					
	QRD-template 7.3.1		QRD-template 8		Model template	
	German	English	German	English	German	English
1 – 10 people from 10000	1.9	3.2	0	0	90.2	97.0
Less than 1 in 1000 but more than 1 in 10000	64.3	82.3	0	1.5	0	0
1 in 1000*	23.0	12.9	97.5	98.5	1.8	0
1 in 10*	0	0	0.6	0	1.2	0
1 in 10000	6.4	1.6	0.6	0	1.8	1.5
1000 to 10000	1.3	0	0	0	0	0
1 to 10 in 1000*	0	0	0	0	2.5	0
10 from 10000*	0	0	0	0	2.5	1.5
1 from 100*	2.5	0	1.2	0	0	0
< 0.1 % – > 0.01 %	0.6	0	0	0	0	0
Number of participants who provided frequencies in numbers	157	62	163	65	163	67

Grey shading shows the method of frequency description used for each template version. * An asterisk indicates overestimation of the frequency compared to the SmPC definition "Rare (≥ 1/10000 to < 1/1000)" (definition in quotation marks taken from [27]).

those with the QRD template 8 in England and for BfArM sample text versions in Germany, and all model template versions ($p \leq 0.045$). The representatives' address list of the marketing authorisation holder (MAH) provided in both QRD template versions was the most common information which participants considered should be deleted (11.0 – 25.5 % of participants depending on leaflet version). Interestingly, 7 participants commended the use of the content list in leaflets using the QRD templates, while 10 participants stated it should be deleted.

4. Discussion

The results provide evidence that QRD template version 8 is an improvement when compared to its previous version, for example, such as due to adding advice to contact healthcare professionals if aspects listed in the "Warnings and precautions" paragraph apply to patients instead of the previous unspecific "take special care" message. The positive study results of QRD template 8 can be transferred to its update, QRD template version 9, and QRD template version 3 intended for non-centralised approved medicines, as they are very similar. One exception, however, concerns the proven beneficial wording contained in QRD template 8 to contact a doctor or pharmacist if any side effects occur. The 2013 implemented new pharmacovigilance legislation caused the QRD template word count in the side effect section to increase by three times in comparison to version 8 [5,8], and it is also unclear whether the integrated request to report side effects actually supports the use of package leaflets. Moreover, the found advantages of the four times shorter model template compared to both tested QRD templates support the raised concerns. As no major disadvantages were found with the short model template, discussions should be initiated to significantly reduce the QRD template word count of headings and general texts. This template condensation will result in necessary shorter package leaflets with the advantages mentioned in the introduction of user friendlier leaflets which motivate reading the provided information and reduce mistrust in the medicine [10].

Strict avoidance of repetitions, such as the information box which provides several duplications which are found in other sections, significantly reduces the length of the QRD template text. The results of both QRD templates illustrate that repetitions relating to pregnancy, breastfeeding, actions if side effects occur and active substance names do not improve package leaflets compared to the model template results. Even though the QRD template states "User testing to date has indicated that most patients value a content listing in the package leaflet." [5] an index is not essential according to the results of this study and some people wished to delete it. Both other model template studies confirm these findings [11,12]. Exclusion

Table 5

Questions relating possible side effects.*

Package leaflet	Average (%)									n
	How many people are affected by a side effect if it is "rare"?			In which of the side effect frequency groups does the following frequency: "affects 5 in 100 people" belong?			What should you do if you notice the side effect runny nose?			
	Correct answers	Wrong answers	Not found answers	Correct answers	Wrong answers	Not found answers	Correct answers	Wrong answers	Not found answers	
English-Model-template-condensed text	100	0	0	85.1	3.0	11.9	82.1	3.0	14.9	67
English-QRD-template-7.3.1-condensed text	95.4	1.5	3.1	63.1	21.5	15.4	26.2	47.7	26.2	65
English-QRD-template-8-condensed text	100	0	0	36.9	33.8	29.2	95.4	1.5	3.1	65
German-Model-template-condensed text	96.0	4.0	0	85.3	2.7	12.0	78.7	6.7	14.7	75
German-QRD-template-7.3.1-condensed text	90.3	5.6	4.2	70.8	22.2	6.9	69.4	15.3	15.3	72
German-QRD-template-8-condensed text	98.6	1.4	0	34.2	31.5	34.2	83.6	1.4	15.1	73
German-Model-template-BfArM text	93.5	2.2	4.3	75.3	7.5	17.2	50.5	6.5	43.0	93
German-QRD-template-7.3.1-BfArM text	90.3	7.5	2.2	60.2	23.7	16.1	55.9	20.4	23.7	93
German-QRD-template-8-BfArM text	92.6	6.4	1.1	29.8	30.9	39.4	69.1	8.5	22.3	94

* Percentages of correct, wrong and not found answers for each package leaflet for questions relating possible side effects.

of information relating prescription status could also be taken into consideration as this is usually already part of the outer packaging. Deleting the list of MAH representatives (a list of currently 30 addresses) would further significantly reduce the QRD template text in package leaflets of centralised approved medicines. Most people assess this information as less important and would exclude it according to this study [20]. Additionally, limitations of spoken languages make it unlikely that patients would contact foreign representatives, and QRD template version 3 also does not recommend such a list for non-centralised approved medicines. Current changes made by the EMA, that the list of MAH representative addresses is no longer a requirement for centralised approved medicines, must be assessed as very positive. It is now acceptable to provide only the relevant local representative, which will be published in the next QRD template update (personal communication, EMA).

Although the QRD template has been used since 1996, reports of large scale studies regarding its readability are scarce and therefore this study focused on testing the template text itself rather than the content of leaflets. Two studies with the short model template, one with 1105 participants investigating ten package inserts and another with 192 participants testing six leaflets, confirm its benefits over the QRD template as found here [10–12]. For example, the study involving 192 participants found on average 18.1 % less time is needed to locate requested information and 15.7 % more information is found or understood when using the model template compared to the QRD template mainly due to template length and difficulties in comprehensibility [11].

While both comparative studies tested QRD templates in the German language valid in the years 2000 and 2008, the study published here provides results with QRD template 7.3.1 and the current QRD template text (with the exception of the two pharmacovigilance implementations relating to side effect reporting contained in version 9). Furthermore, this study is the first to illustrate that the shorter model template also has advantages in English and for a long package leaflet text. It can be expected that similar benefits exist in other European languages; however, that requires further investigation.

The written readability test method was chosen to test the templates to simulate as far as possible a real life situation whereby a patient reads a package leaflet and answers questions in the questionnaire without any assistance. This method has been developed to provide identical study conditions without external influences such as those due to interviewers' mimics and gestures which is essential to compare different leaflet texts. It has been validated in a previous study and is accepted by all medicine approval agencies in the European Union [12, 15]. A three to four times higher number of people tested each package leaflet in this study than the Europe wide recommended minimum number of 20 participants [15]. Moreover, every participant was intended to test each investigated template in a cross-over study design which has a positive influence on study results. An identical type size and face, paper and print quality including layout of information were used in both countries for the tested package leaflets and the questionnaire thereby further allowing comparison of the tested templates.

The model template was superior to both tested QRD templates regarding the number of correct answers when participants were asked to locate information in section 2. Although the new subheading in QRD template 8 of "Warnings and precautions" combined with a reference to healthcare professionals was significantly better than the imprecise "Take special care" subheading in QRD template 7.3.1, the corresponding heading in the model template "Consult your doctor before taking X in the case of" enabled participants to provide more correct information. Other authors also have reported comprehensibility problems with the heading "take special care" as participants are unsure what that means [11, 21].

Three methods of describing frequencies of side effects were tested in this study. The model template used the recommendations made by the German agency BfArM [22] and the EMA, as well as patients and consumer organisations which were published in 2007 [23] after being developed and successfully tested in the above mentioned readability test study with 1105 participants [12]. Leaflets with QRD template 7.3.1 used the verbal and numerical text published in the first Readability Guideline [24], and leaflets with QRD template 8 used the version provided in the current annotated template version [25] where it states "…user testing has shown that double sided expressions such as 'affects more than 1 in 100 but less than 1 in 10' are not well understood and should not be used." [5]. However, data which support this quotation has not been published by the QRD group.

Results provided in Tables 4 and 5 show that the cited double sided frequency explanations used in QRD template 7.3.1 leaflets caused comprehensibility problems. But the QRD group is wrong in its general denigrating of "double sided expressions" as can been seen by the results of the model template frequency explanation. Moreover, when participants in this study were asked to identify in which frequency group a side effect belongs if it affects 5 in 100 people, QRD template 8 frequency explanations illustrated the worst comprehensibility.

The results of the PAINT3 study investigating 295 package inserts with 5091 participants confirm the findings of this study relating to the current QRD template frequency explanation valid since version 8 was published. This explanation possesses a significantly lower rate of comprehensibility compared to the version used in the model template [26].

Another important issue illustrated in Table 5 is that people overestimate the current QRD template side effect frequency explanation compared to the SmPC explanation and this by up to a factor of 10. For example, if a side effect affects 1 in 10 000 people it would be classified as rare, but nearly all subjects incorrectly believed in the case of QRD template 8 according to Table 5 that such a side effect applies to 1 in 1 000 people.

The way of presenting the frequencies of side effects (either as a table at the start of section 4 or as part of the list) was found in this study not to produce any significant differences between template versions regarding comprehensibility as over 90 % of participants could locate how many people were affected by a rare side effect. However, using side effect frequencies as subheadings and subsequently listing the corresponding side effects brings both contents advantageously in near proximity.

Knowing how to take appropriate actions is important if any side effects should occur, but the longer wording in QRD template 7.3.1 led many patients in this study to believe that a healthcare professional should only be contacted "If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet." This occurred also in other studies [11, 12]. QRD template 8 caused the most correct answers and can therefore be welcomed as an improvement with the exception of the text extension in QRD template 9 already explained above.

5. Conclusion

The results from this study show that it is possible to improve the QRD template. When taking into consideration that user testing is mandatory for all package leaflets of medicines distributed within the European Union, an obligation to conduct readability tests and publish results

Pharm. Ind. 76, Nr. 8, 1312–1322 (2014)

of new QRD template versions before they are used would be advantageous for users.

Keeping the QRD template as concise as possible should be of major priority in the future as this study showed that reducing the number of template words by using the model template does not reduce the usability of package leaflets. Moreover, a shorter QRD template would definitely be beneficial in terms of locatability and comprehensibility of the information provided in package leaflets. Marketing authorisation holders and regulatory agencies should strictly abide by the bracketing convention in the QRD template and exclude all non-mandatory information until a shorter template can become effective.

LITERATURE

[1] ERGO, FORSA. Verständlichkeit von Informationen. *http://www.ergo.com/de/Presse/Overview/Pressemappen/Verstaendlichkeitsstudie/~/media/ERGOcom/PDF/Studien/Verstaendlichkeitsstudie/ERGO-Verstaendlichkeitsstudie-Ergebniss-2012.ashx.* Accessed July 27, 2012.

[2] Raynor D, Knapp P, Moody A, Young R. Patient information leaflets – impact of European regulations on safe and effective use of medicines. *The Pharmaceutical Journal.* 2005;275:609-11.

[3] European Parliament and Council of the European Union, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. *Official Journal of the European Communities.* 2001;L311:67-128.

[4] European Medicines Agency. Product information templates. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jsp*&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022c59&jsenabled=true. Accessed August 13, 2012.

[5] European Medicines Agency. QRD Human Product Information Templates; Centralised procedures – version 8 – 22.07.2011; MR/DC/Referral procedures – version 2.0 – 30.08.2011. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jsp*&mid=WC0b01ac0580022c59&murl=menus/regulations/regulations.jsp&jsenabled=true. Accessed September 2, 2011.

[6] The European Parliament and the Council of the European Union. Directive 2010/84/EU of the European Parliament and the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Communities.* 2010, L348:74-99.

[7] The European Parliament and the Council of the European Union. Regulation (EU) No. 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Regulation (EC) No. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No. 1394/2007 on advanced therapy medicinal products. *Official Journal of the European Communities.* 2010, L348:1-16.

[8] European Medicines Agency. QRD Human Product Information Templates; Centralised procedures – version 9 – 15.03.2013; MR/DC/Referral procedures – version 3.0 – 11.04.2013. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jsp*&mid=WC0b01ac0580022c59. Accessed August 13, 2013.

[9] Wolf A, Fuchs J, Schweim H. QRD Template Texts Intended for Package Inserts / Development from the first QRD template up to the new draft of July 2012. *Pharm Ind.* 2012;74:1540-9.

[10] Fuchs J. The way forward in package insert user tests from a CRO's perspective. *Drug Information Journal.* 2010;44(2):119-29.

[11] Fuchs J, Scheunpflug C, Götze E. The influence of the European Union's QRD template on the use of package inserts compared with a shorter model template. *Pharm Ind.* 2012;74:126-36.

[12] Fuchs J, Hippius M. Inappropriate dosage instructions in package inserts. *Patient Education and Counseling.* 2007;67:157-68.

[13] Bundesinstitut für Arzneimittel und Medizinprodukte. Muster für Fach- und Gebrauchsinformationen. *http://www.bfarm.de/DE/Arzneimittel/2_zulassung/verfahren/mufag/mufagDb/mufagdb-node.html.* Accessed August 10, 2011.

[14] European Parliament and Council of the European Union, Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Union.* 2004; L136:34–57.

[15] Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human. Position paper on user testing of package leaflet – consultation with target patient groups (Compliance with article 59(3) of Council Directive 2001/83/EC). February 2011. *http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_234_2011.pdf.* Accessed August 3, 2012.

[16] European Commission, Directorate General. A guideline on the readability of the labelling and package leaflet of medicinal products for human use. Brussels: European Commission, Revision 1, 12 January 2009. *http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf.* Accessed July 17, 2011.

[17] Diehl J, Staufenbiel T. Statistik mit SPSS für Windows Version 15. 1st edition. Verlag Dietmar Klotz; 2007.

[18] Horn M, Vollandt R. Multiple Tests und Auswahlverfahren. Stuttgart, Jena, New York: Gustav Fischer Verlag; 1995.

[19] European Commission. VOLUME 3B. Guidelines. Medicinal products for human use. Safety, environment and information. Excipients in the label and package leaflet of medicinal products for human use. *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf.* Accessed July 29, 2011.

[20] Fuchs J, Banow S, Görbert N, Hippius M. Importance of package insert information in the European Union. *Pharm Ind.* 2007;69:165-72.

[21] Andriesen S. Readability Testing of PILs – a new 'must'. *European Pharmaceutical Contractor.* Autumn 2006:42-4.

[22] Bundesinstitut für Arzneimittel und Medizinprodukte. Wie sollen die Häufigkeiten für Nebenwirkungen in der Produktinformation angegeben werden? *http://www.bfarm.de/SharedDocs/4_FAQ/DE/Arzneimittel/pal/ja-ampal-faq.html?nn=1014336.* Accessed August 15, 2011.

[23] European Medicines Agency. Minutes of the third meeting of the EMEA human scientific committees' working party with patients' and consumers' organisations (PCWP). *http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2009/12/WC500019989.pdf.* Accessed August 13, 2012.

[24] European Commission. A guideline on the readability of the label and package leaflet of medicinal products for human use. Brussels, 29. September, 1998. *http://www.alims.gov.rs/download_eng/regulativa/gl981002.pdf.* Accessed June 9, 2012.

[25] European Medicines Agency. QRD Human Product Information Annotated Template version 8. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jsp*&mid=WC0b01ac0580022c59&murl=menus/regulations/regulations.jsp&jsenabled=true. Accessed July 17, 2011.

[26] Fuchs J, Götze E, Scheunpflug C. Update des QRD-Templates und daraus resultierende Änderungen in Packungsbeilagen und Fachinformation. *Pharm Ind.* 2011;73:670-8.

[27] European Medicines Agency. Product information templates. Appendix II: MedDRA (version 12.0) terminology to be used in Section 4.8 "Undesirable effects" of SmPC. August 2010. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jsp*&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022c59. Accessed July 17, 2011.

Chefredaktion: Claudius Arndt. Sekretariat: Gudrun Geppert. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Tel.: +49 (0) 75 25 94 00, Fax: +49 (0) 75 25 94 01 80. e-mail: redaktion@ecv.de. http://www.ecv.de. Herstellung: Rombach Druck- und Verlagshaus GmbH & Co. KG / Holzmann Druck GmbH & Co. KG.