Implementation of the European QRD Template in Package Leaflets of Centralized Approved Medicines

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Abstract

Background: Package leaflets of medicines distributed within the European Union should use the template headings and standard texts created by the Working Group on the Quality Review of Documents (QRD). The following study investigated how the QRD template is implemented in this patient information. *Methods:* All English-language package leaflets available on the European Medicines Agency website for centralized authorization procedures were downloaded 3 times, separated by a time period of 1 year. A catalog of criteria was applied to analyze QRD template text use. *Results:* Because of the rapid implementation of updates, the template text used in each package leaflet (N = 565) increased from an average of 444 words in the first download to 565 words during the 2 subsequent years. With template version 7, the fraction of template text per leaflet was 19.7% in 2011, which increased to 21.5% in 2013 with implementation of version 9. *Conclusions:* Limitation to mandatory contents through stricter use of the QRD template's bracketing convention, which would reduce package leaflets' text without loss of essential information, is suggested. In addition, making the current QRD template more concise is strongly recommended.

Keywords

QRD template, package insert, package leaflet, regulatory affairs, patient information

Introduction

Package leaflets are important patient information and must be provided with all medicines distributed within the European Union (EU).[1–3] The content and presence of a package leaflet for a particular medicine was originally determined by the national ruling of the country where it was brought onto market. This later changed for countries in the EU when the Union's legislation replaced national rules concerning package leaflets' content and order of information. Directive 92/27/EEC[4] made the presence of a package leaflet mandatory for each medicine distributed within the EU.

With the intention of harmonizing the structure and wording of this patient information in the EU and connected countries (Norway, Liechtenstein, and Iceland), the Working Group on the Quality Review of Documents (QRD) was established in June 1996 by the European Medicines Agency (EMA).[5] This group published the first edition of the QRD template in the same year. The QRD template, which is based on Article 65 of Directive 2001/83/EC,[3] covers general requirements for the summary of product characteristics, labeling, and the package leaflet of medicines. Fourteen updates have followed since publication of the first edition of the template for medicines approved via the centralized procedure, up to version 9.1 in June 2015.[6] The QRD template itself is a text framework that provides headings for paragraphs and subparagraphs and includes standard statements applicable for the broad range

of all distributed medicines. Medicine-specific information is inserted into this text frame by the pharmaceutical companies. The QRD template for centralized procedures is available in the 23 official EU languages with the addition of Icelandic and Norwegian and aims to support the pharmaceutical industry in providing user-friendly product information.

Centralized procedures came into operation in 1995,[7] allowing applicants to obtain a marketing authorization that is valid throughout the EU, Norway, Liechtenstein, and Iceland. A slightly modified version of the QRD template for centrally approved medicines is available for medicines approved via a mutual recognition (MR) or decentralized procedure (DC).[5] Using the QRD template has the advantage that patients find identical, standardized headings and general texts, including the same order of information in package leaflets in each EU member state plus the 3 above-mentioned associated countries.

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Submitted 14-Aug-2015; accepted 4-Nov-2015

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According to the "Consolidated Versions of the Treaty on EU and of the Treaty Establishing the European Community," article 249, the QRD template is only a guidance document and is therefore not legally required to be implemented.[8] However, it is stated on the first page of the annotated QRD template version 9.1 that standard statements given in the template "must be used whenever they are applicable." Deviation is possible in certain cases to accommodate specific medicinal product needs and will be considered on a case-by-case basis.[5]

During development of QRD template version 8 for centralized approved medicines and version 2 for medicines authorized by other procedures in 2011, headings and mandatory texts underwent major changes based on information gained from user testing and feedback from various sources such as agencies, the pharmaceutical industry, and academia, as well as patient and consumer groups.[9] QRD template version 9 and its updated version 9.1 provide several further text additions as a result of the latest pharmacovigilance legislation.[5,10,11] Since the first QRD template was published in 1996, its volume of text required for the package leaflet has expanded from 94 words to 840—an approximately 9-fold text increase.[6] However, the negative effects of this increased volume of QRD template text have not been addressed in version 9.1, although previous studies have shown the advantages of a shorter template of around 200 words, mainly through avoiding repetitions and long sentences.[6,12,13] Moreover, use of the QRD template is one main reason for increasing package leaflets' text volume, with the negative outcome that increasing the number of words significantly decreases: (1) locatability of provided information, (2) motivation to read package leaflets, and (3) trust in using required medicines.[12-14]

Although the QRD template has been in use since 1996, studies regarding how it is implemented in package leaflets have not yet been published. To fill this data gap, this study aimed to investigate how the QRD template is utilized in terms of wording and how rapidly updates are adopted in package leaflets.

Methods

We downloaded all English-language package leaflets of centralized approved medicines available on the EMA website[15] between October 21 and 23, 2011. The second download took place on October 3, 2012 and the third on October 7, 2013. Package leaflets of medicines that were marked on the EMA website as withdrawn postapproval, suspended, or refused were not investigated. For the second and third downloads, only package leaflets that were present in the first download and had been updated or unchanged, and leaflets of medicines with valid approval, were again integrated into the analysis. The downloaded PDF files of each package leaflet were converted into Word 2007 documents (Microsoft Corp) for further analysis using the software Acrobat 9 Standard (Adobe Systems Inc). Leaflets impossible to convert into Word files were excluded to ensure uniform data analysis.

The following criteria, developed from our previous research results,[6,12] were used to assess each package leaflet:

- Type of medicine: pharmaceutical form, prescription status, Anatomical Therapeutic Chemical (ATC) code
- Total word count per package leaflet
- QRD template words per package leaflet according to the black printed QRD template text[5]
- QRD template version
  The differences in the 6 main headings of package leaflets were used to distinguish between QRD templates 7 and 8, and the new QRD template version 9 paragraph regarding the reporting of side effects was used to determine if this version was present. Although 5 different subversions of QRD template 7 exist, none of the minor differences affected analyzed elements; therefore, a division into subeditions of this template version was unnecessary.
- Wording used in the *general information list* at the beginning of each package leaflet and in the content list
- QRD template wording used in package leaflet *headings or general texts* of the 6 main sections, for example:
  - Wording relating to contraindication in the case of an allergy to ingredients
  - Presenting side effects and side effect frequency explanation
  - Presence of list of marketing authorization holders' representatives, including the word count of this list

A "yes" or "no" decision was made as to whether the different QRD template elements were provided in the examined leaflets, and if "yes," the wording of which template version 7, 8, or 9 was present. The word count was determined using the "Word count" tool of the Word 2007. All data were coded and analyzed using a pivot table in Excel 2007 (Microsoft Corp) and the SPSS statistic program (version 18.0; IBM Corp). As related samples were investigated, nonparametric tests were required. The Wilcoxon signed-rank test was used to evaluate differences in word counts between downloads and QRD templates used, whereby the sign-test was used to evaluate the wording changes.

Results

Of the 616 package leaflets that were initially downloaded in 2011 according to the Methods section, we could only analyze 565, as 51 leaflets could not be converted into Word files. Calculation of the 95% confidence intervals showed that the initial group of 616 leaflets was always between the upper and lower limits of the confidence interval ranges for the 565 package leaflets in terms of the following criteria:

- sales status RX or OTC
- pharmaceutical forms (5 groups, each with the predefined minimum 10% of leaflets)

Table 1. Number of Words in Total per Package Leaflet and Their QRD Template Fractions of the 3 Downloads of Centralized Approved Medicines.

	Download 1: QRD Template 7 (n = 565)	Download 2: QRD Template 7 (n = 382)	Download 2: QRD Template 8 (n = 183)	Download 3: QRD Template 7 (n = 170)	Download 3: QRD Template 8 (n = 278)	Download 3: QRD Template 9 (n = 81)
Percentage of package leaflets of ... (%)	100	67.6	32.4	32.1	52.6	15.3
Number of words per package leaflet	799 to 6249 (average 2437)	808 to 7776 (average 2502)	1119 to 6437 (average 2672)	1115 to 7822 (average 2451)	1078 to 6437 (average 2710)	1189 to 4990 (average 2751)
Word count caused by QRD template (without list of MAH representatives)						
Minimum words	256	286	289	314	289	408
Maximum words	596	623	627	591	610	643
Average words	444	450	509	451	509	565
Percentage of total words (%)	6.7 to 39.4 (average 19.7)	6.4 to 39.9 (average 19.6)	7.2 to 34.1 (average 20.5)	6.7 to 39.0 (average 20.0)	7.2 to 38.2 (average 20.3)	11.9 to 34.8 (average 21.5)

- drug classification according to ATC code (first level of the anatomical main group)

Authorization dates of the package leaflets from download 1 ranged from October 1995 to October 2011, and there were up to 38 revisions of the documentation. At the time of the first download, QRD template version 7 was the oldest identified template edition according to the defined criteria, and all examined package leaflets had used version 7.

At the time of the second and third downloads, 423 and 411 package leaflets had been updated, respectively, since the previous download. In the third download, 36 medicines had been withdrawn or suspended. Consequently, their package leaflets were removed from the third data set.

Despite the high rate of updates per year of 74.9% in the second and 77.7% in the third download, newly published QRD template versions were not always implemented in each updated package leaflet (see Table 1, first row of data).

At the time of the first download, 98.9% of analyzed package leaflets were from medicines available only on prescription, and the remaining 6 were over-the-counter (OTC) products. The most common type of medicines according to pharmaceutical form were for parenteral administration (injections and infusions: 37.0%) and film-coated tablets (26.9%). When examining the first level of the anatomical main group of the ATC code for medicines in the first download, "antineoplastic and immunomodulating agents" were most commonly represented (19.6%), followed by "antiinfectives for systemic use" (15.9%).

Total Word Count and QRD Template Words in Package Leaflets

The total number of words in the examined leaflets from the first download was on average 2437 words, which increased to 2542 words in the second and 2639 words in the third download (averages for all package leaflets regardless of template version used). This is a significant text increase of 8.3% within 2 years ($P < .001$ for text increase between each download).

In addition, the average number of template words per leaflet significantly increased with increasing version number, from 444 words in the first download with version 7 to 565 words in the third download with version 9 ($P < .001$; Table 1), causing an approximately 10% word count increase of template text per leaflet after each template update. Moreover, the average percentage of template text per leaflet significantly increased with each update, from 19.7% in 2011 in the case of version 7 to 21.5% in 2013 in leaflets with version 9 ($P < .001$). This illustrates that the QRD template fraction in the package leaflet, which contains only general contents, causes an increase in package leaflet text volume more rapidly than medicine-specific information.

The last QRD template 7 version (7.3.1) contains 638 words, whereas version 8 contains 771 words and version 9 contains 840 words.[16] Leaflets from the first download used an average of 69.6% of the QRD template 7.3.1 text; in the second download, this fraction was 66.0% in leaflets using version 8, and in the third download it was 67.3% in the case of version 9.

In the following section, results are presented for package leaflet sections with QRD template text changes between versions 7 and 9.

QRD Template Text at the Beginning of Package Leaflets

In each download, all examined leaflets contained the recommended QRD template general information list at the start of the leaflet, but 6 leaflets did not contain the subsequently designated content list; both have been part of the QRD template since 1998. Of the 81 leaflets using version 9, there were 21 that had the black symbol for "additional monitoring" resulting from Directive 2010/84/EU.[10]

Some QRD template text is presented in the template in pointed brackets and is only intended for optional use. Template version 7 offers the optional choice of the words "doctor" and/or "pharmacist" in bullet point 2 of the general information list at the beginning of the package leaflet. This was extended with the additional choice of "nurse" in version 8.[9] Table 2 shows a significant trend to the longer version as a

Table 2. Percentage of Package Leaflets Downloaded from the EMA Website and Assessed According to Terms Used for Health Care Professional in the Second Bullet Point of the General Information List Provided at the Beginning of Leaflets.

Terms Used in Bullet Point 2: "If you have any questions ask your . . ."	Percentage Package Leaflets With the Wording Provided in the Left Column					
	Download 1 (n = 565)	Download 2: QRD Template 7 (n = 382)	Download 2: QRD Template 8 (n = 183)	Download 3: QRD Template 7 (n = 170)	Download 3: QRD Template 8 (n = 278)	Download 3: QRD Template 9 (n = 81)
Doctor	8.7	10.2	5.5	9.4	7.2	7.4
Doctor or pharmacist	82.6	78.3	58.5	81.2	55.4	61.7
Doctor, pharmacist or nurse	5.2	6.3	33.9	6.5	32.7	27.2
Doctor or nurse	1.6	2.9	0.5	2.4	3.6	2.5
Other wording	2.0	2.4	1.6	0.6	1.1	1.2

result of implementation of QRD templates 8 and 9 ($P < .001$). Package leaflets from the second and third downloads with "doctor," "pharmacist" or "nurse" in bullet point 2 also used this longer version in other template texts, with a frequency of up to 7 times per leaflet.

The 6 main headings used to assess the implemented QRD template version are mirrored in the content list. However, 6 of the 565 examined content lists in the first download did not completely conform to the QRD template, as instead of the standard 6 sections, section 4, for example, was used for information for diabetics. Consequently, the information normally included in sections 4 to 6 was moved to sections 5, 6, and an additional section 7. In 4 other cases, point 7 was also included in the content list for further information or patient instructions.

Two package leaflets in all 3 downloads contained subheadings in the content list, which increased the number of words for the standard index from approximately 36 to 161 words in one case, and in the other to 149 words.

QRD Template Text in Package Leaflet Section 2

In section 2 of the package leaflet for template version 7, patients were told not to use the medicine if they were "allergic (hypersensitive) to the active ingredient or any of the other ingredients."[17] In versions 8 and 9, the term "allergic" is used alone.[5,9] Of the examined leaflets with version 8 in the second download, 79.7% had used the term "allergic" alone, according to version 8. In the third download, the percentage of leaflets using versions 8 or 9 which used the term "allergic" alone was 75.1% and 84.0%, respectively, illustrating a significant change to leaflets using template version 7 ($P < .001$; Table 3).

Since template versions 8 and 9, the contraindication point in the case of an allergy to an ingredient contains a cross-reference to section 6 to tell patients where the other ingredients are listed.[5,9] Although all leaflets in the first download used template version 7, 39.1% had already included a reference. However, wording here varied between leaflets but in many cases the patient was told directly to refer to section 6, or alternatively "the list of ingredients contained at the end of the leaflet." In the second download, this increased to 89.1% of the leaflets that had used version 8 and in the third download to about 90% when version 8 or 9 had been used ($P < .001$; Table 3).

The next heading in the QRD template, section 2, is "Take special care with X" in version 7,[17] which was changed in version 8 to "Warnings and precautions."[5,9] Of the 183 leaflets in the second download using version 8, 92.9% had used the heading "Warnings and precautions," and of the 359 leaflets in the third download with versions 8 or 9, 93.5% and 92.6% used the updated heading, respectively—again a significant change since the first download ($P < .001$; Table 3).

Under the heading "Other medicines and X," the standard warning statements differ between QRD template 7 and 8/9. In version 7, the patient is told to "Please tell your <doctor> <or> <pharmacist> if you are <taking> <using> or have recently <taken> <used> any other medicines, including medicines obtained without a prescription,"[17] whereas since version 8 the sentence has been altered to "Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines."[9] In the second download, 62.3% of leaflets with version 8 had used the updated wording, whereas 27.9% still included the sentence from version 7. In the third download, around 70% of the leaflets with versions 8 and 9 had the updated statement, whereas 20.9% of leaflets with version 8 and 24.7% of leaflets with version 9 still retained the statement from version 7. The remaining leaflets had a statement that did not conform to either version. The wording change between templates and downloads was again significant ($P < .001$; Table 3).

Since publication of QRD template version 8, for example, the word "alcohol" is optional in the subheading of the section for interactions with "Food and drink," and the word "fertility" in the section subheading for "Pregnancy and breast-feeding." We analyzed the use of these terms. One-quarter of package leaflets in the second and third downloads used the term "fertility" in the subheading; however, 58.7% of these provided no information on fertility in the second download and 67.8% in the third. Of leaflets that used the term "alcohol" in the subheading, 10.5% in the second download and 11.1% in the third download provided no information on alcohol.

Under the subheading for pregnancy and breast-feeding is an optional standard sentence in QRD templates 7, 8, and 9. The wording differs between each version: whereby version 7 states "Ask your doctor or pharmacist for advice before taking

Table 3. Analysis of Package Leaflets of Centralized EU-Approved Medicines Regarding Text Elements in Section 2 of the Package Leaflet.

	Percentage of Package Leaflets of ...					
Terms Used in Section 2 of the Package Leaflet	Download 1: QRD Template 7 (n = 565)	Download 2: QRD Template 7 (n = 382)	Download 2: QRD Template 8 (n = 183)	Download 3: QRD Template 7 (n = 170)	Download 3: QRD Template 8 (n = 278)	Download 3: QRD Template 9 (n = 81)
Contraindication subsection						
"allergic (hypersensitive)"	100	100	20.3	99.4	24.9	16.0
Just "allergic"	0	0	79.7	0.6	75.1	84.0
Reference to section 6	39.1	40.8	89.1	38.8	89.9	93.8
Warnings/precaution subsection						
Use of subheading "Take special care"	100	100	3.3	98.8	4.7	4.9
Use of subheading "Warnings and precautions"	0	0	92.9	1.2	93.5	92.6
Interactions with medicines subsection						
Use of sentence from template 7: "Please tell your <doctor> <or> <pharmacist> if you are <taking> <using> or have recently <taken> <used> any other medicines, including medicines obtained without a prescription"	96.8	96.9	27.9	92.4	20.9	24.7
Use of sentence from template 8/9: "<Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines>"	0	0	62.3	1.2	69.8	69.1
Use of sentences from both templates (template 7 and 8/9)	0	0	1.6	0	1.8	1.2
Use of no template conform interaction sentence	3.2	3.1	8.2	6.5	7.6	4.9
Interactions with food/drink subsection						
Use of term "alcohol" in subheading	0.8	0.8	10.4	1.2	9.0	13.6
Pregnancy/breast-feeding subsection						
Use of term "fertility" in the subheading	0.2	0.3	25.1	0	23.0	33.3
Use of sentence from template 7: "Ask your doctor or pharmacist for advice before taking any medicine"	52.6	53.7	20.8	51.8	18.3	13.6
Use of sentence from template 8/9: "If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine"	0	2.9	41.5	6.5	45.7	40.7
Use of sentences from both templates (template 7 and 8/9)	0	0	2.2	0	2.9	2.5
Use of no template conform pregnancy and breast-feeding sentence	47.4	43.4	35.5	41.8	33.1	43.2

any medicine,"[17] versions 8 and 9 extend this advice to "If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine."[5,9] Table 3 shows the frequency with which each statement was used for leaflets containing a relevant subheading, with significant changes between downloads (*P* < .001).

QRD Template Text in Package Leaflet Section 4

Recommendations relating to side-effect frequency explanations have been published in the QRD template since version 8, where it is advised that these explanations "should not appear

before the list of side effects as this takes up space and has been shown in user testing to be misleading to patients."[5,9] Leaflets with version 7 mostly provided frequency explanations in a table or list at the beginning of the side effect section, which has significantly changed in leaflets using newer templates (*P* < .001). Over 74% of leaflets using the latter versions presented them as part of the side effect list, where a particular frequency explanation is noted followed by a record of all side effects in that frequency category (Table 4). A significant change was also seen for the location of where severe side effects are presented, which since version 8 is recommended to be at the start of the side effect section (*P* < .001; Table 4).

Table 4. Analysis of Package Leaflets of Centralized EU-Approved Medicines Regarding Presentation of Side Effect Frequency Explanations.

	Percentage of Package Leaflets of ...					
	Download 1 Using QRD Template 7 (n = 565)	Download 2 Using QRD Template 7 (n = 382)	Download 2 Using QRD Template 8 (n = 183)	Download 3 Using QRD Template 7 (n = 170)	Download 3 Using QRD Template 8 (n = 278)	Download 3 Using QRD Template 9 (n = 81)
Presentation of severe side effects at first	46.4	51.6	74.3	52.9	73.7	79.0
Presentation of side effect frequencies						
In table or list at start of side effect section	49.4	51.3	7.7	45.9	10.4	23.5
As part of the side effect list	46.9	44.5	90.7	47.6	88.8	74.1
Other form of presentation	3.7	4.2	1.6	6.5	0.8	2.4
Method of frequency description of side effects						
"Common: affects 1 to 10 users in 100" (BfArM,[18] EMA 2007[19])	67.0	66.7	17.6	59.4	16.2	15.0
"Common: may affect up to 1 in 10 people" (QRD template 8/9)[5,9]	15.0	17.6	76.4	23.6	79.1	80.0
"Common: less than 1 per 10 but more than 1 per 100" (Readability Guideline 1998[25])	10.5	8.3	3.3	6.7	0.7	0
Other frequency explanation	7.5	7.4	2.7	10.3	4.0	5.0

The majority of package leaflets which used QRD template 7 contained the side-effect frequency explanation type recommended by Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)[18] and EMA[19] in 2007 (Table 4). Publication of version 8 resulted in a rapid and significant change in leaflets using newer templates to the explanation type provided in their annotated versions ($P < .001$; Table 4).[5,9]

List of Local Representatives of the MAH in Section 6

The list of local representatives of the Marketing Authorization Holder (MAH) in the QRD template must not necessarily be included at the end of the package leaflet according to the investigated templates, but when it is present, addresses must be included for all listed countries (30 at the time of QRD template version 9 publication[5]). In the first, second, and third downloads, 82.3%, 84.2%, and 85.8% of the investigated package leaflets, respectively, contained this list, where it accounted for up to 33.6% of the leaflet's word count. On average, the list of MAH representatives contributed to 13.0%, 12.8%, and 12.4% of the leaflets' word count in the first, second, and third downloads, respectively.

Discussion

Implementation of the QRD template within the EU, Iceland, Norway, and Liechtenstein creates uniform general contents, headings, and order of information in package leaflets, which aims to benefit patients in that they receive the same leaflet structure and wording independent of which medicine or country. This is in contrast to some other countries such as the United States, where 3 different types of patient information exist using different layout and content.[20]

According to the calculation of the 95% confidence interval provided above, the analyzed sample of 565 package leaflets and the results obtained can considered to be representative for all centralized approved medicines published on the EMA website in October 2011. Different results for medicines approved via other procedures (DC, MR, and national procedures) within the European Economic Area (EEA) could be possible, as these products have usually been available for longer on the pharmaceutical market, and only one, or a selection of EEA countries, are involved in their regulatory procedures. This could result in fewer updates of package leaflets being required in comparison to new substances, which are often approved via centralized procedures. Furthermore, the duration of regulatory procedures could be longer for these processes in comparison to centralized procedures, which could also influence the frequency of updates.

Nevertheless, the results of this study based on a representative example of investigated package leaflets of centralized approved products highlight that pharmaceutical companies and authorities strive to produce up-to-date documents. This is supported by the result that three-quarters of the examined package leaflets were updated within each year analyzed. However, it must be mentioned that not all updated leaflets used the last published QRD template version. The duration of approval procedures and procedure-specific requirements are 2 reasons for the newest template version not being implemented in full (or used at all) at the time of submission of the update to the authorities. Some pharmaceutical companies may have taken parts of new template draft versions into consideration, which

could explain why a larger fraction of leaflets with version 7's main headings already used wording published in later template versions, such as side-effect frequency explanations.

We chose the package leaflets of centralized approved medicines, as these were publicly available documents and enabled a large and representative sample for a wide variety of medicines. As only package leaflets for centralized procedures were analyzed, differences in template implementation in those authorized for purely national procedures cannot be excluded because some member states still have their own specific requirements for national legislation. However, as the QRD template should also be used for national procedures, existing national requirements are placed increasingly in the background. Differences in QRD template use for products authorized via MR or DC procedure must also be considered; however, they are minimal, and it is also not known how quickly the package leaflets are altered or updated for MR, DC, or national procedures compared to those for centralized approved procedures. The QRD template for MR, DC, and national procedures version 3.1 only differs from that for centralized approved procedures in the less important information in section 6 of the package leaflet, where it includes a section for the names of the medicinal product and member states of the EEA where it is authorized, and does not include the optional list of MAH representatives.

The average number of words per package leaflet found in this study is around 20% higher than that ascertained in an analysis of a representative sample (N = 271) of all German package leaflets from the year 2005.[14] It must also be taken into consideration that the package leaflets examined were mainly for prescription-only products rather than OTC products. The PAINT2 study showed that package leaflets for OTC have on average fewer words than those for prescription-only products.[14] According to the results provided above, the increasing volume of text in the QRD template is a main reason for the continuous increase in package leaflet length, even though it does not contain specific contents regarding the respective medicine. Similarly to this study, the above-mentioned analysis of German package leaflets[14] found that an average of 17.7% of their volume of text was caused by the QRD template and that over a 5-year period the word count of template text in the examined 271 package leaflets increased by 25.1%. However, the QRD template text fraction per leaflet decisively increased to 21.5% in centralized approved medicines when using version 9 (see Table 1).

The results provided in this article show that pharmaceutical companies use on average two-thirds of the QRD template text in each leaflet. While some package leaflets contain almost the complete QRD template (see Table 1), other leaflets were found to use less than half of the template, as the template's bracketing convention had been carefully applied and optional text had been excluded. All investigated package leaflets were approved by the authorities, and leaflets with a template word count close to the minimum according to Table 1 contain a similar number of words to a developed, optimized template with 200 words,[12] which has been successfully readability tested in different studies with a total of 6437 participants.[12,21–23] This means that from regulatory as well as scientific perspectives, a QRD template significantly shorter than the current version is conceivable, which would reduce the average word count of all package leaflets by a minimum of 10%.

Moreover, both patients and health care professionals strongly favor more concise package leaflets than those we have today,[1,2] and each decrease in the number of words used in package leaflets significantly increases (1) patients' motivation to read package leaflets, (2) their trust in using required medicines, and (3) the locatability of provided information as already mentioned at the beginning of this article.[12,13,22,23] This shows the inevitable importance of reducing the volume of QRD template text, such as by avoiding repetitions, as this would improve each package leaflet used within the EU and connected countries.

All leaflets examined in this study contained a list of general information at the start, which was followed by an index. However, this QRD template section of up to 110 words[5] is not a requirement in any EU or national directive. This could be removed from the QRD template, especially as most of the sentences are repeated elsewhere. The description of what the leaflet is for and why it has been supplied has also been suggested to be superfluous, as package leaflets have been provided for a long time within the EU and it can reasonably be assumed that patients are familiar with such documents. Readability test studies with the above-mentioned, shorter, 200-word model template that does not contain this information box have demonstrated that leaflets containing this general information have no benefit when compared to those without it.[12,21,23]

Use of all optional terms such as "alcohol" and "fertility" in subheadings also contributes to the text volume. These terms are superfluous and should be avoided, especially in package leaflets, which do not provide information regarding either fertility or alcohol, a fact which pharmaceutical companies and agencies should be made aware of.

According to QRD template version 9.1, the list of 30 local marketing authorization holder representatives is no longer essential, and only local representatives of the respective member country should be provided.[5] Although inclusion of this list was noncompulsory, over 80% of examined leaflets contained it, which contributed to an average of 12.4% to 13% of package leaflet word count. Its omission can be seen as an improvement, especially as it does not provide any medicine-specific information, significantly increases the volume of text, and is unimportant for both patients and health care professionals.[2,14]

Informing users about the risk of side effects from their medicines is vital to enable patients to make informed decisions about their medicine taking.[24] The green explanatory text in the annotated template versions 8 and 9 states that a combination of verbal terms and numerical data should be used to describe the frequency of side effects, and that user testing has shown that double-sided expressions such as "affects more than 1 in 100 but less than 1 in 10" (from the Readability

Guideline published in 1998[25]) are not well understood.[5,9] However, data that support this opinion has not been published by the QRD group.

Before QRD template 8, the recommended frequency explanation was that published in 2007 by BfArM[18] and EMA,[19] which is based on the PAINT1 study results.[21] The analysis of package leaflets downloaded from the EMA website showed that the method of describing frequencies of side effects rapidly changed during the examined time period to that contained in the newer template versions, indicating that the pharmaceutical industry follows the recommendations provided by the QRD template.

However, it has been shown that although the frequency explanations published since QRD template 8 are short, they are poorly comprehensible. In a 2014 published study where 241 participants were asked to identify in which frequency group a specific side effect belonged, QRD template 8 frequency explanations (which is the same as that contained in versions 9 and 9.1) showed the worst comprehensibility and led to overestimations of frequencies by up to 10% that a particular side effect could occur.[23] An analysis of the wrong answers given by participants showed that the main problem was that the provided numerical explanation could not be assigned to the correct frequency group. The results of a further readability test study investigating 295 German package leaflets with 5091 participants supports these findings relating to the inferiority of the current frequency explanation. In the latter study, the side-effect frequency explanations recommended by BfArM[18] and EMA[19] in 2007 were found to have a 10% higher comprehensibility rate than those in the QRD template since version 8.[26] The presented results from the described studies indicate that the QRD group is wrong in its general negative opinion relating to using double-sided frequency expressions. However, it can be postulated that the frequency explanations in the current QRD annotated template are more comprehensible than those published in the Readability Guideline from 1998, as they are shorter and have less complex phrasing.[26]

The most preferred method of displaying side-effect frequencies was as a separate table or list at the beginning of the side effect section for package leaflets using QRD template 7. This changed with introduction of QRD templates 8 and 9, where frequency descriptions of side effects were incorporated into the list of side effects in over 74% of package leaflets with these template versions. This change can be welcomed as positive, as it reduces the space needed to print the side effect section, and using side-effect frequencies as subheadings and subsequently listing the corresponding side effects brings both in proximity, making it easier for the user to understand the frequency with which the listed side effects occur.

In this context, the rapid implementation of QRD template updates into package leaflets leads to improved patient information according to the results provided above, positive aspects being, for example, displaying the frequency explanation in the list of side effects. However, if suboptimal recommendations are part of the QRD template, the shown fast updating can also cause a step backwards, as can be seen in the case of the currently used wording of side-effect frequency explanations. It must be mentioned critically that the QRD template was not revised here in versions 9 and 9.1, although both quoted studies relating to the frequency explanation wording were known to the responsible authorities. A prompt amendment in the next update should correct this.

Conclusions

Most of the QRD template texts are used in package leaflets; however, the pharmaceutical industry and authorities should pay more attention to only using the essential template parts. To keep package leaflets concise, the current QRD template should be significantly shortened, which would improve all package leaflets in each country where the template is implicated. In addition, template amendments must be based on sufficient research evidence, and exposed errors should be eliminated as quickly as possible.

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