QRD Template Texts Intended for Package Inserts

Development from the first QRD template up to the new draft of July 2012

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ABSTRACT

Since the first QRD template was published in 1996, the number of words used in this text frame of headings and general package insert texts has increased extensively from initially less than 100 to over 800 words in the new draft from July 2012. During development of the 14 versions, headings and mandatory texts have undergone major changes as well as their required order defined in Directive 2001/83/EC amended by Directive 2004/27/EC. The following article investigates and assesses in detail, changes in the QRD template for the package insert up to the present day.

ZUSAMMENFASSUNG

QRD-Templates für Packungsbeilagen / Entwicklung vom ersten QRD-Template bis zum neuen Entwurf vom Juli 2012

Seitdem das erste QRD-Template im Jahr 1996 publiziert wurde, ist die Wortanzahl dieses Textrahmens von in der Packungsbeilage einzusetzenden Überschriften und allgemeinen Texten extrem angestiegen: von ursprünglich weniger als 100 auf über 800 Wörter des neuen Entwurfs vom Juli 2012. Während der 14 Templateversionen hatten die Überschriften und obligatorischen Texte viele Änderungen erfahren, wozu auch die in der Direktive 2001/83/EG enthaltene und durch die Direktive 2004/27/EG angepasste Reihenfolge der Gliederung gehört. Der nachfolgende Artikel untersucht und bewertet detailliert die Änderungen des QRD-Templates für die Packungsbeilage bis zum heutigen Tag.

KEY WORDS

- Package insert
- Package leaflet
- QRD group
- QRD template
- Readability guideline
- Readability test

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1. Introduction

When Directive 92/27/EEC came into force in 1999, it became mandatory that a patient information leaflet was provided with all medicines distributed within the European Union (EU) [1]. This information – also known as the package insert – should enable patients to use their medicines properly and create awareness of when to seek further medical advice.

With the intention of harmonising the structure and content of this product information, the Working Group on the Quality Review of Documents (QRD) was established in June 1996 by the European Medicines Agency (EMA) [2] which published the first edition of the QRD template in the same year covering the summary of product characteristics, labelling of the product and the package insert of medicines. Twelve updates followed for medicines approved via the centralised procedure up to the latest draft version in July 2012. A slightly modified version is available for mutual recognition (MR) and decentralised procedures (DC), the only differences being the absence of the Marketing Authorisation Holder's (MAH) local representatives address list and other further information in the last section of the package insert [3]. More extensive templates are also provided for certain product groups such as radiopharmaceuticals [4].

The QRD template itself is a text framework which provides headings for paragraphs and sub-paragraphs including standard statements applicable for the broad range of distributed medicines. Medicine specific information is inserted into this text frame by the pharmaceutical company.

The QRD template is available in the 22 official EU languages with the addition of Icelandic and Norwegian and aims to support the pharmaceutical industry in providing user friendly product information. Using this template has the advantage that patients find identical standardised headings and general texts, including the same order of information, in package inserts in each European Union member state plus Iceland, Liechtenstein and Norway [2].

According to the "Consolidated versions of the treaty on European Union and of the treaty establishing the European community", article 249,

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the QRD template is only a guidance document and therefore not legally required to be implemented into practice [5]. However, the QRD template states on the first page of the annotated version 8 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 [10]. Newer versions of the QRD template use a bracketing convention and different colour text for certain information (Table 1).

The QRD template version 8 of the package insert published in 2011 is the first version that reflects information gained from user testing and is based on feedback from various sources, such as agencies, the pharmaceutical industry and academia as well as patient and consumer groups. Furthermore, the update also takes into account the new legal requirements which have come into force since the previous revision. For example, the package insert now includes information on the benefits of the medicine, its use in children and a reorganised side effect section [10]. The above mentioned user testing results are a collection of reported specific problems identified in the previous QRD template version 7.3.1. Implementation of the QRD template published in 2011 should be as soon as possible but no later than 1st July 2014 [6,7]. However, the QRD template draft published in July 2012 again provides new text as a result of the latest pharmacovigilance legislation. For the package insert, this means introduction of a black symbol and a standardised explanatory statement at the beginning of the leaflet for medicinal products subject to additional monitoring, and a further paragraph encouraging patients to report side effects in section 4 [8–10]. In the following article, the development of the QRD template is analysed up to the new draft version.

2. Materials and methods

QRD template versions 1 to 7.3 in English were kindly provided by the EMA, while versions 7.3.1. and 8, including the draft of July 2012, were downloaded from the EMA website [10, 11].

Table 1

Symbols and text colours used in the annotated QRD template 8 [10].

Symbol/ text colour	Meaning
{text}	Information to be filled in
text	Text which must be used
<text>	Text to be selected or deleted as appropriate
X	"X" stands for the (invented) name of the medicinal product
[Orange text]	Cross-refer to the section / information of the SmPC
[Green text]	Explanations

The black QRD template text in English intended for package inserts of centralised approved over-the-counter (OTC) medicines was analysed regarding the number of words using the word count tool of Microsoft Office Word 2007. The bracketing convention allows for large amounts of black text to be omitted. The minimum word count strictly followed this principle and all optional information was deleted including storage conditions in package insert section 5. The maximum word count showed the number of words when all information possible contained in the black printed QRD template text is integrated in the package insert. However, the list of the 29 local representatives was not considered for the analysis. In cases of "<take><use>" or similar versions, only one word was counted as only one term should be used in the package insert. In addition, the number of long sentences, repetitions and abbreviations used in the black QRD template text was calculated. According to the readability guideline of 1998, a sentence was assessed as a "long sentence" if it contained more than 20 words [12]. Furthermore, information in black text of each section was analysed to illustrate the QRD template changes and development up to the current date. Text passages coloured orange or green, as seen in the QRD template text colour convention illustrated in table 1, were not considered in the investigation.

3. Results

Between 1996 and the new QRD template draft of July 2012, 8 main versions of the QRD template have been published. Taking into account revisions which were undertaken, the number of adopted QRD templates – including the new draft – totals 14.

3.1. Number of QRD template words

The first two published versions of the QRD template included only twelve section headings which literally reflected the information required by article 7 of Directive 92/27/EEC which was in force at that time [1]. No general advice or subheadings were provided that should be used verbatim in package inserts, therefore the number of words used in both template versions was only 94 (Fig. 1). Although the QRD template version 3 was based on the same Directive as both predecessors, it had already taken on a form similar to that which we recognise today using main and subheadings plus general texts. Apart from that:

- the number of main section headings was reduced to five,
- the name of the medicine was inserted in template headings and texts using the placeholder "X",
- texts to be used optionally were enclosed in pointed brackets,
- explanations were provided using green ink.

These changes caused the number of words to increase greatly as seen in Fig. 1 and reflected the package insert example of the first Readability Guideline which was also published in September 1998, as was QRD template version 3 [12]. The increase in the maximum number of words was plainly greater than the minimum number of words as shown in Fig. 1, a situation which applies up to the new draft published in July 2012.

QRD template versions 4 to 6.1 were published between August 1999 and July 2004. Template version 6 was the

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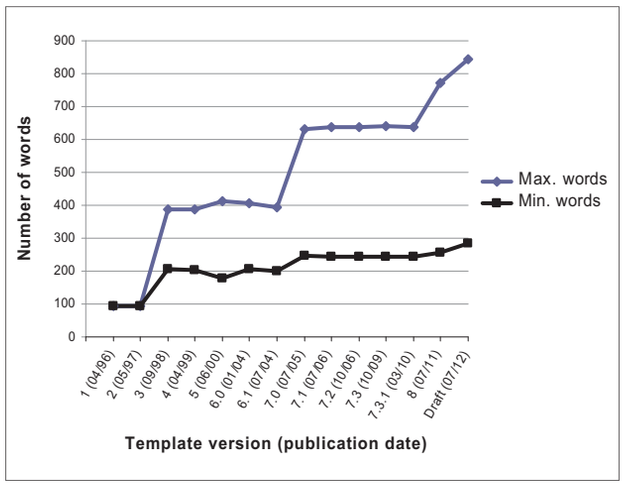

Fig. 1: Minimum and maximum words used in the QRD templates intended for package inserts of centralised approved OTC medicines.

earliest to include information in the package insert as required by Directive 2001/83/EC [13]. In version 6.1, orange text was used for the first time to cross-refer to sections in the Summary of Product Characteristics (SmPC) which should be reflected in that particular section in the package insert. The QRD template version 7.0 was published in 5 different editions between 2005 and 2010 and was the earliest to be available as an annotated and non-annotated edition on the EMA website. In the advisory text at the start of QRD template version 7.0 (published July 2005) it was stated that applicants had to make sure that the package insert was made available in formats appropriate for the blind and partially sighted reflecting article 56 (a) of Directive 2004/27/EC [14]. Furthermore, the new order of information published in this Directive was considered, for example, all ingredients had to be listed in the final section of the package insert instead of at the beginning. QRD template 8 (published in July 2011) is the most recent and shows many changes in the package insert when compared to its predecessor 7.3.1 [10]. Detailed explanations are given in green text in all sections and cross references to the relevant sections in the SmPC are continually provided in orange. Many more subheadings are present such as regarding use in children and adolescents reflecting changes which were previously made to the SmPC in QRD template version 7.3.1. This is stated in QRD template version 8 to be an attempt to make it easier for the patient to navigate their way through the package insert. Pointed brackets are used more frequently in version 8 meaning that more standard statements are optional than in previous templates which could result in a reduction in the minimum number of template words required for package inserts, but Fig. 1 shows the outcome to be the opposite.

The new QRD template draft published in July 2012 offers an amendment for medicinal products which are subject to additional monitoring. This is in the form of a black symbol (which has yet to be decided on), and an appropriate related explanatory text [10]. The information box at the start of the package insert should also include a cross-reference to section 4 to aid the user in locating possible side effects. A standard sentence in section 4 further encourages users to report any adverse reactions. These new text passages are due to the implementation of the pharmacovigilance legislation and have again increased the text volume in the template (Fig. 1, Tables 2 and 5) [8–10].

3.2 Number of repetitions, long sentences and abbreviations used in the QRD template

Avoid long sentences of over 20 words in length and abbreviations are two recommendations of the first Readability Guideline of 1998 [12]. Repetitions should also be eliminated as this leads to an increase in the volume of text. All versions of the template – except 1 and 2 – use sentences of over 20 words and recurring information. While versions 3 to 6.0 only used one repetition of the same content, this number increased to two in version 6.1, three repetitions in versions 7.0 to 7.3.1 and four since version 8. A similar trend was seen in the number of long sentences, with two sentences of over 20 words in QRD template versions 3 to 6.1 and three in versions 7.0 to 7.3.1. However, version 8 showed an improvement with only one long QRD template sentence while the draft published in July 2012 raised this to two.

Abbreviations are only found at the end of the package leaflet in version 7.0, with "EMEA" and in version 8 "EU/EEA" (European Union/European Economic Area). The abbreviation used for the expiry date has also been recommended since version 7.0.

3.3 Development of package insert sections in the QRD template

This section demonstrates the development of the QRD template beginning from its first version up to the new draft of July 2012 using selected parts as examples.

3.3.1 Information box at the beginning of the package insert

The first two versions of the QRD template provided no information box or index for the beginning of package inserts, but began with all active substances and excipients subsequent to the name of the medicine. From version 3, an information box was present at the start of the package insert template which distinguished between prescription only (Rx) and medicines available without prescription. The bracketing convention means that the information can be adapted to the product requirements i. e. to reflect whether the medicine is only administered by a doctor or bought by the patient. Strictly speaking, the brackets could also be interpreted to mean

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Table 2

QRD template texts to be used after the name of the medicine and active substances at the beginning of the package inserts for OTC medicines. (Changes in comparison to the predecessor are highlighted in grey.)

QRD template version				
3–4	**5–6.1**	**7.0–7.3.1**	**8**	**Draft from July 2012**
----------			----------	<{Black symbol} This medicine is subject to additional monitoring. This is to allow any safety information on the medicine to be identified rapidly. You can help by reporting any side effects you may get (see section 4).>
<Read all of this leaflet carefully because it contains important information for you.			Read all of this leaflet carefully before you start <taking><using> this medicine because it contains important information for you.	
This medicine is available without prescription, for you to treat mild illness without a doctor's help. Nevertheless you still need to use X carefully to get the best results from it.	This medicine is available without prescription. Nevertheless you still need to use X carefully to get the best results from it.	This medicine is available without prescription. However, you still need to <take><use> X carefully to get the best results from it.	Always <take><use> this medicine exactly as described in this leaflet or as your <doctor><,><or><pharmacist><or nurse><has><have> told you.	
Keep this leaflet. You may need to read it again.				
Ask your pharmacist if you need more information or advice.				
You must see a doctor if your symptoms worsen or do not improve after {number of} days.>		You must contact a doctor if your symptoms worsen or do not improve <after {number of} days.>	If you get any side effects, talk to your <doctor><,><or><pharmacist><or nurse>. This includes any possible side effects not listed in this leaflet.	If you get any side effects, talk to your <doctor><,><or><pharmacist><or nurse>. This includes any possible side effects not listed in this leaflet. See section 4.
----------		If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your <doctor><or><pharmacist>.>	You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days>.>	

that the entire box is optional which would cause a reduction of around one hundred template words. The wording in the information box is the same in versions 3 to 6.1. Following some changes, versions 7.0 to 7.3.1 were also identical. However, differences are seen in the information box depending on whether a product is OTC or Rx. In version 8, a user who has been prescribed a medicine is told to ask a doctor, pharmacist or nurse for more information, whereas the consumer of an OTC preparation is only told to consult a pharmacist. The user of a prescription medicine is also told not pass it on to others which is not required for OTC medicines. In version 8, the MAH is actively instructed not to include this sentence for Rx products only used in a hospital setting. If an OTC product has been bought the consumer is advised to consult a doctor if the condition does not improve after a certain number of days.

The draft version from 2012 includes a cross-reference to section 4 for the location of side effects although such a cross reference to section 4 has been shown in results from readability testing not to be necessary [16]. The draft QRD template from July 2012 also introduces for the first time a black symbol for medicinal products subject to additional monitoring (Table 2). For OTC medicines, the statement that "This medicine is available without prescription" is omitted from version 8 for reasons which are not defined.

Of interest is that the starting sentence and the advice to keep the leaflet are the only sentences of the information box not found elsewhere in the QRD template version 8 making this box, to a great extent, redundant.

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Reasons why these repeats are absolutely necessary are not provided in the template.

3.3.2 Development of section headings

All versions of the QRD template with exception of versions 1 and 2 start with a contents list after the information described in section 3.3.1 above. The annotated QRD template version 8 states that user testing has shown that an index is valued by patients, although user testing research illustrates that package inserts without one are not at a disadvantage [10, 17, 18].

For QRD template versions 3 to the draft of July 2012, the headings of sections 1, 3 and 4 use the same wording. In version 5, section 6 was included for using the heading "Further information". The heading of section 2 was altered in version 8 into "What you need to know before you <take><use> X" and that of section 6 into "Contents of the pack and further information", to provide the reader with more details about the content to be expected in both sections (Table 3).

3.3.3 QRD template text recommendations for package insert section 2

In the indication section, the QRD template from versions 3 to 7.3.1 recommended only one black printed sentence which was for optional use only – "This medicine is for diagnostic use only." This was deleted in version 8 and the following was newly inserted: "You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days." – a verbatim repetition of the last bullet point of the information box used for OTC medicines.

Section 2 is usually the largest in the package insert and therefore the use of carefully worded subheadings is crucial to aid the patient in finding relevant information.

Template versions 3 up to the draft of July 2012 started with contraindications listed under "Do not <take> <use> X" (Table 4). The statement under "Do not <take> <use>" informs patients not to use the medicine if an allergy to one of the ingredients exist. Beginning with the wording "hypersensitivity (allergy)" used in version 3, this text was amended in version 7.0, and corrected in version 8 as the term hypersensitivity is not completely correct here. For example, a hypersensitivity to lactose does not automatically mean a contraindication to products which contain this ingredient [15]. However, QRD template version 8 and the new draft still use the word "hypersensitivity" in the SmPC section 4.4. The contraindication section of the SmPC does not therefore conform with the package insert as stipulated by Directive 2001/83/EC, article 59 and must be amended as soon as possible to fulfil this ruling [13].

Warnings and precautions are provided under the next section 2 subheading which read up to version 7.3.1 "Take special care with X". This was changed in version 8 to the "Warnings and precautions" subheading followed by the mandatory advice according to the template's bracketing convention that patients should contact healthcare professionals if listed aspects apply to them. This clear instruction can be seen as an improvement in comparison to the unspecific advice of "take special care" [19]. Other additions in the QRD template version 8 are inclusion of alcohol in the food and drink subheading and the insertion of fertility in the pregnancy and breast-feeding section if facts are known. The amended subheading "X contains {name of excipient(s)}" emphasises any excipients which need to be drawn to the user's attention.

3.3.4 Dosage instruction and administration error texts

In QRD templates 1 and 2, section 8 was designated to contain the "Instructions for proper use", while from QRD template version 3 onwards, package insert section 3 is for dosage instructions – advice on dosage, method and duration of use – followed by three subsections relating to administration errors – overdose, missing a dose and stopping treatment. Black printed subheadings have only been present since QRD template version 3 for the three administration error sections. The subheading "Use in children" has been part of the QRD template since version 7.3.1 and was changed in QRD template version 8 to "Children and adolescents". General advice with almost identical wording has been provided in black ink for the start of section 3 since QRD template version 5 which informs patients to

Table 3

Development of QRD template main section headings to be used in package inserts.

QRD template version	Section 1	Section 2	Section 3	Section 4	Section 5	Section 6
3–4	What X is and what it is used for	Before you <take><use> X	How to <take><use> X	Possible side effects	Storing X	–
5–6.1						Further information
7.0–7.3.1					How to store X	
8 and draft of July 2012		What you need to know before you <take><use> X				Contents of the pack and further information

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Table 4

Subheadings (in bold) and standard statements (normal type) used in section 2 of the QRD template. (Changes in comparison to the predecessor are highlighted in grey.)

Template version			
3–6	**6.1**	**7.0–7.3.1**	**8 and draft July 2012**
Do not <take><use> X			
<if you are hypersensitive (allergic) to {active substance} or any of the other ingredients of X>		<if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of X.>	<if you are allergic to {active substance(s)} or any of the other ingredients of this medicine (listed in section 6).>
Take special care with X			**Warnings and precautions**
<if you ....>			Talk to your doctor <or><pharmacist><or nurse> before <taking><using> X
–			**Children and <adolescents>**
	<Taking><Using> other medicines		**Other medicines and X**
		<Please tell your <doctor><or><pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.>	<Tell your <doctor><or><pharmacist> if you are <taking><using>, have recently <taken><used> or might <take><use> any other medicines.>
<Taking><Using> X with food and drink			**X with <food><and><,><drink> <and><alcohol>**
Pregnancy **Breast-feeding**		**Pregnancy and breast-feeding**	**Pregnancy <and><,> breast-feeding <and fertility>**
<Ask your doctor or pharmacist for advice before taking any medicine.>			<If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your <doctor><or><pharmacist> for advice before taking this medicine.>
Driving and using machines			
Important information about some of the ingredients of X			**<X contains {name the excipient(s)}>**
<Taking><Using> other medicines*			
<Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed>			

* Double use of "<Taking><Using> other medicines" in version 6.1 is probably a mistake in the template.

always use the medicine as the doctor has instructed and to check with the doctor or pharmacist if they are unsure.

QRD template version 8 provides slightly different wording to be used in the case of OTC medicines. Moreover, this version provides the first time three black printed sentences for optional use relating to the divisibility of tablets depending on the appearance of the score line.

3.3.5 QRD template side effects' text

Section 9 of QRD templates 1 and 2 contained the heading "Description of undesirable effects under normal use" and Directive 92/27/EEC instructed that the actions to be taken must be explained if side effects should occur, including the communication of undesirable effects to the doctor or pharmacist, especially if they are not mentioned in the package insert [1]. This general advice has been printed in black since QRD template version 3 including a second general sentence to be written at the beginning of package insert section 4 that all medicines can cause side effects (Table 5).

Only since QRD template version 8, has the patient been advised to contact healthcare professionals if any side effects occur and an optional subheading regarding children and adolescents is inserted. Previous template versions recommended that patients should contact an expert if the side effect gets serious or is not listed in the package insert. This caused patients to understand that they should not contact healthcare professionals in the case of a side effect which is listed in the package insert [18].

The draft template from July 2012 suggests the new subheading in section 4 "Reporting of side effects", followed by a mandatory text where the patient is actively encouraged to report any symptoms to different national contacts, when they are believed to be side effects of using the medicine.

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Table 5

QRD template standard statements intended for use in package insert section 4. (Changes in comparison to the predecessor are highlighted in grey.)

QRD template version			
3–6.1	**7.0–7.3.1**	**8**	**Draft of July 2012**
Like all medicines, X can have side effects	Like all medicines, X can cause side effects, although not everybody gets them.	Like all medicines, this medicine can cause side effects, although not everybody gets them.	----------*
–	–	<Additional side effects in children <and adolescents >>	
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.	If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor><or><pharmacist	If you get any side effects, talk to your <doctor><or><,><pharmacist><or nurse>. This includes any possible side effects not listed in this leaflet.	If you get any side effects, talk to your <doctor><or><,><pharmacist><or nurse>. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly to the national reporting system via the internet at {insert link to the relevant 'national reporting system website'}; or you can report via {insert alternative ways of reporting}. By reporting side effects you can help provide more information on the safety of this medicine.

* This text component is not contained in the QRD template draft from July 2012.

Apart from the changes in the black QRD template text, the green explanations, which have been provided in this section since the annotated QRD template version 8, note that serious side effects should be listed first with clear handling instructions for the patient, followed by a list of other side effects arranged according to descending frequencies. This method reflects advice contained in the readability guideline [12]. A frequency convention for side effects has also been recommended since QRD template 8 (annotated version), where MedDRA system organ classes (SOCS) should not be used as the latter uses terms unfamiliar to patients [20, 21].

The wording for the side effect frequency explanation recommended for use in the SmPC chapter 4.8 (double sided e. g. "common (≥ 1/100 to < 1/10)" does not conform with that of the annotated QRD template version 8 intended for the package insert, which is closed on one side only e. g. "common, may affect up to 1 in 10 people". Again this is a discrepancy with respect to Directive 2001/83/EC, article 59 as the contents of both documents must be in accordance with each other [13].

However, the side effect frequency explanations published by the EMA in 2007 e. g. "common, affects 1 to 10 users in 100" are in compliance with the frequency explanation recommended for the SmPC [23]. Furthermore, readability test studies – one with 1105 participants investigating 10 package inserts and another with 5091 participants investigating 295 package inserts show that the EMA side effect frequency explanations published in 2007 have a greater than 10 % higher comprehensibility rate than the version contained in the current QRD template version 8 [18, 22].

3.3.6 Storage and further information

In the first two QRD templates, section 10 was designated for reference to the expiry date, storage precautions and visible signs of deterioration. Since QRD template version 3 was developed, section 5 was to be used for this storage information and instruction on keeping the medicine out of sight and reach of children. The advice to store medicines away from children was omitted in versions 6.0 and 6.1 for unnamed reasons and information relating to disposal of no longer required medicines has been part of the QRD template since version 7.0. The statements contained in section 5 have undergone slight changes mainly of an editorial nature since they were initially published. Standard storage statements were originally included in the QRD template until version 6.0 when these were put into an appendix.

Section 6 was originally not included in versions 3 to 5 of the QRD template as the information which is now presented here had to be provided during the currency of these versions before the indication section according to Directive 92/27/EEC [1]. Versions 6.0 and 6.1 provided in the sixth section a list of local MAH representatives and information relating to the last approval of the package insert. Up to date, this list has always been optional but where one MAH representative address is presented, the addresses of all EU/EEA countries must be included.

The change in the information provided in section 6 caused by Directive 2004/27/EC was seen the first time in QRD template version 7.0 [14]. Since this time, information relating to active substances, excipients, description of the product, contents of the pack, the MAH and manufacturer must be provided at the end of the package insert. The date of last approval was changed in version 8

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to the last revision even though this has been a requirement since Directive 2001/83/EC came into force [13]. After this date, three standard statements were included from QRD template version 7.0 onwards. The first should be used for medicines approved under "conditional approval" and states that more evidence is to come about the medicine, and the second is for authorisations under "exceptional circumstances" for example due to the rarity of the disease. The third statement is intended for all centralised approved medicines and notes the EMA website for more detailed information about the medicine. Subsequent to these three statements, information for healthcare professionals can be presented since QRD template version 5; however, this is not compulsory.

4. Discussion

4.1 Assessment of QRD template development

Use of the QRD template ensures European uniformity in the organisation and content of package inserts due to observing an identical order of information in all EU/EEA countries as well as headings, subheadings and general texts. In addition, this text frame is independent of the type of medicine described in the package insert, whereby only marginal differences exist between OTC and Rx medicines, as well as between centralised, decentralised or nationally approved products. This guarantees that patients find an identical structure in all package inserts which is an advantage in comparison to other countries, such as the United States of America where three different types of patient information are used: consumer medication information, patient package inserts and Medication Guides [24]. The continuous update of the QRD template has led to improvements. For example, version 8 shows in comparison to its predecessor version 7.3.1, clearer headings and instruction for patients relating to precautions and warnings, and the number of long sentences and passive sentences has been reduced as recommended in the Readability Guideline from 2009 [20]. However, the current actual QRD template still contains some weaknesses. The mentioned discrepancies between the texts intended for package inserts and SmPC in the contraindication section – allergy versus hypersensitivity – and the side effect frequency explanations, are aspects which require improvement as soon as possible. This is of particular importance as pharmaceutical companies which strictly follow the QRD template in both package inserts and SmPC thereby conflict with article 59 of Directive 2001/83/EC which requires that both documents "...shall be drawn up in accordance..." [8].

The large increase in the number of QRD template words required in package inserts must be recognised as a negative trend, because pharmaceutical companies use, and are often invited by agencies, to provide almost all black printed QRD template texts shown as the maximum curve in Fig. 1. This is a key reason for the steady increase in volume of package inserts and conflicts with the interests of patients and healthcare professionals as both strongly favour more concise package inserts [25–27].

Moreover, increasing the number of words used in package inserts significantly decreases patients'

- motivation to read the package inserts,
- trust in using the medicine,
- ability to locate the provided information [28, 29].

These facts are of exceptional significance, as the QRD template text frame only provides general information, and the use of a shorter template of around 200 words shows considerable advantages in comparison to the QRD template – meaning discussion relating to compression of the template text should be initiated [17]. Before a shorter QRD template can be published, we recommend that pharmaceutical companies should consequently abide by the bracketing convention in the template to achieve the minimum number of QRD template words in package inserts as illustrated in the blue curve of Fig. 1, which the authorities should permit the industry to do. Furthermore, omitting the list of MAH's local representations which contains 29 addresses greatly reduces the volume of package inserts – in particular of less important information [25].

4.2 Assessment of the QRD template draft

The QRD template draft published in July 2012 shows a further text increase which again augments the volume of package inserts with the adverse consequences explained. The recently provided texts are based on the new EU pharmacovigilance legislation, which were in principle defined with the well-meant intention to increase the safety in using medicines [8, 9]. However, we the authors of this article must voice our concerns regarding the success of a black symbol for medicines requiring special monitoring and the invitation to patients to report side effects directly to the authorities.

Providing a black symbol with the startling statement that the "...medicine is subject to additional monitoring ... You can help by reporting any side effects you may get." may give patients the feeling of being a test person used to investigate an unsafe product. The result will be that patients are deterred from using required medicines. When considering that the shelf life of medicines may be up to 5 years, this could also lead to misinformation if the pharmaceutical company was able to remove the black symbol from its product information after a year and a patient receives the product some months before the shelf life ends.

The opportunity for laymen to report side effects, such as via the internet, without assistance by healthcare professionals also raises our concerns because differentiation between side effects caused by a medicine, consequences of a certain disease, other medicines, dietary habits, use of stimulants, weather or multiple other factors already pose difficulties for healthcare professionals. This strategy of laymen reporting will lead to very insubstantial facts and vast difficulties are expected in the implementation of these data in future product information such as in company core data sheets (CCDS), SmPCs and package inserts.

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Furthermore, a package insert is created to advise patients. Using package inserts for other aspects, such as increasing the number of side effect reports, deflects from the key intention of informing patients on the correct use of medicines.

However, the new pharmacovigilance legislation demands a statement in package inserts relating to reporting of side effects, therefore, only a very short sentence should be included in the QRD template in which only one contact should be provided until reconsideration of deleting this requirement. Any reference to national differences is irrelevant to patients and the intention of reporting side effects, and should therefore be excluded.

5. Conclusion

QRD template development can be seen as positive due to improvements in general headings and standard sentences. However, according to the explanations provided above, the template text intended for package inserts should be restricted to that which is really necessary to inform patients regarding effective and safe use of medicines. Keeping the template as concise as possible should be of major priority in the future.

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