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Statement relating to the

QRD template draft

(status of discussion: 12th of July 2012)

content

1 Introduction

The Quality Review of Documents (QRD) Working Group published the second draft of an updated QRD human product information template on 12th of July 2012 (EMA/468496/2912); following on from their initial draft of 10th of April 2012 (EMA/204889/2012) [1, 2]. Any differences between both QRD template drafts are very minor. The main reason for the revision is the implementation of the new pharmacovigilance legislation published in Directive 2010/84/EU and regulation (EU) No 1235/2010 [3, 4]. This applies especially to:

- **Additional monitoring**

  Directive 2010/84/EU provides the following new requirements relating to medicines that require additional monitoring, in paragraph 10: "Medicinal products subject to additional monitoring should be identified as such by a black symbol and an appropriate standardised explanatory sentence in the summary of product characteristics and in the package leaflet." Furthermore, Directive 2010/84/EU amends article 11 of Directive 2001/83/EC: "For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary of product characteristics shall include the statement: 'This medicinal product is subject to additional monitoring'" [3].
- **Encouragement of reporting of side effects**

  Directive 2010/84/EU further enhances article 11 of Directive 2001/83/EC thus: "For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a(1), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Article 107a(1).' [3]."

  In addition, the SmPC shall ask healthcare professionals to report any suspected side effect in accordance with the national spontaneous reporting system.

The QRD template draft of July 2012 provides the following open questions for comment:

- The location of the black symbol and of the explanatory statement for medicinal product subject to additional monitoring.
- The wording of the explanatory statement for medicinal product subject to additional monitoring.
- The location and wording of the standardised text to encourage reporting of adverse reactions.

In the following, we at PAINT-Consult® again avail of the opportunity to offer our thoughts in relation to the new QRD template draft. This we do on the basis of our experiences gathered

as a provider of SmPC, package insert and readability test services to the pharmaceutical industry. Furthermore, these comments are borne by scientific experience in these fields since 1999 and our experience as pharmacists in working with healthcare professionals and patients.

2 Amendments relating to medicines that require additional monitoring

2.1 SmPC amendments concerning additional monitoring

The QRD template draft provides the following text at the beginning of the SmPC section:
"[For medicinal products subject to additional monitoring ONLY:
The black symbol and the statements should only appear preceding section 1]

<{Black symbol*} This medicinal product is subject to additional monitoring. This is to allow any safety information to be identified rapidly. Healthcare professionals are encouraged to report any suspected adverse reactions. See section 4.8.>

1. NAME OF THE MEDICINAL PRODUCT

[For medicinal products subject to additional monitoring ONLY:
The black symbol should only appear preceding the invented name in the section 1]

<{Black symbol}>{(Invented) name strength pharmaceutical form}"

The two paragraphs preceding the section heading "1. NAME OF THE MEDICINAL PRODUCT" explain the purpose of the black symbol in the case of medicines subject to additional monitoring. Providing an explanation at the beginning of the QRD template - it follows that this should also be provided at the same place in the SmPC - does not benefit SmPC users; especially as the symbol must be repeated in the SmPC section 1. We contend that any explanation would be more appropriate only in the respective section, thereby avoiding a repeat of the symbol.

The current QRD template draft favours positioning the black symbol in front of the medicine name in SmPC section 1. We believe this is also inappropriate, as this symbol has no connection with the product name and could lead to misinterpretations of that ilk. The black symbol should be provided and explained on a separate line in section 1 of the SmPC. Based on our research and readability test experience, the black symbol explanation should be shortened to the first of the three suggested sentences as the other two offer no further

information, or simply repeat the new wording suggested for SmPC section 4.8. Furthermore, only the first sentence is required according to Directive 2010/84/EC. Therefore we recommend the following wording at the beginning of the annotated QRD template for the SmPC considering the bracketing and colour convention; and no further text relating to the black symbol should be provided before the SmPC section 1:

1. NAME OF THE MEDICINAL PRODUCT

[Guidance on the expression of strength is available in the "QRD Recommendations on the Expression of Strength in the Name of Centrally Authorised Human Medicinal Product (as stated in section 1 of SmPC and in the name section of labelling and PL".]

{(Invented) name strength pharmaceutical form}

[No ® ™ symbols attached here; "tablets" and "capsules" to be presented in the plural form throughout the text.]

[For medicinal products subject to additional monitoring ONLY: The black symbol and the explanatory statement should be presented on a separate line in section 1]
<{Black symbol} This product is subject to additional monitoring.>

2.2 Package insert amendments concerning additional monitoring

The QRD template draft provides the following text for package inserts, at the beginning:

"**Package leaflet: Information for the <patient> <user>**

[For medicinal products subject to additional monitoring ONLY:
The black symbol should only appear preceding the invented name in the title]

<{Black symbol}> {(Invented) name strength pharmaceutical form}
{Active substance(s)}

<{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).>

[* NOTE to be included in the annotated version of template: Standard statements given in the template must be used whenever they are applicable. If the applicant needs to deviate from these headings/statements to accommodate medicine-specific requirements (e.g. for medicines for children administered by parents, "you may get" could be replaced by "your child may get"), alternative or additional statements will be considered on a case-by-case basis.]

<**Read all of this leaflet carefully before you start <taking> <using> this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your <doctor> <,> <or> <pharmacist> <or nurse>.
<- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.>
- 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.

<**Read all of this leaflet carefully before you start <taking> <using> this medicine because it contains important information for you.**
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.
- 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.
- You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days>.>"

Identically to the SmPC, the black symbol should not be part of the medicine name as this may be misunderstood by patients to be part of this name. Furthermore, many pharmaceutical companies use specific design elements at the beginning of a package insert. Using the black symbol as suggested in the QRD template draft will only conflict with these. Also, it is important that the black symbol be presented in tandem with the explanatory statement to aid patients' understanding of same; this also renders inappropriate the use of said symbol ahead of the medicine name.
Based on the explanations provided, we suggest providing the black symbol, together with its explanatory statement, in a fifth bullet point in the list before the index.

The explanatory statement and any other texts used in the QRD template should be as short as possible, as the Directive 2001/83/EC amended by Directive 2010/84/EU requires only the following short sentence: "This product is subject to additional monitoring." Moreover, package insert wording must be kept to a minimum, as any increase in the number of words is known to significantly decrease patients'

- motivation to read the package insert
- ability to locate the provided information
- confidence to use the medicine [5-7]

Therefore, the explanatory statement can and must be shortened. Using just the sentence stating that "This product is subject to additional monitoring." is acceptable, while a cross-reference to section 4 of the package insert, including text concerning reportage of side effects, is not required in the explanatory statement. The same applies to the cross-reference "See section 4" in the fourth bullet point in the general statements for medicines only available on prescription and in the third bullet point for OTC products. This cross-reference

is not necessary according to our readability test results, gathered in research studies and tests conducted on behalf of companies operating in the pharmaceutical sphere.

In addition, the note inserted in the QRD template draft relating to general use of the QRD template text should be deleted as the same information is already contained on the first page of the current QRD template, where it is stated that “Standard statements are given in the template, which must be used whenever they are applicable. If the applicant needs to deviate from these statements to accommodate medicinal product-specific requirements, alternative or additional statements will be considered on a case-by-case basis.” [8]. The same message is also contained in the readability guideline published in 2009 [9].

Therefore, we recommend the following wording at the beginning of the annotated QRD template for the package insert, considering the bracketing and colour convention:

Package leaflet: Information for the <patient> <user>
[Heading to be printed]

{(Invented) name strength pharmaceutical form}
{Active substance(s)}
[The (invented) name of the medicine (referred to as “this medicine” throughout the package leaflet, wherever practical) followed by the strength and pharmaceutical form (i.e. as it appears in section 1 of the SmPC) should be stated here in bold. This should be followed by the active substance(s) (as stated on the label section 1), which may be written on the line below. In the remainder of the document the invented name should appear in lower case without bold or underline and should not be used excessively throughout the text.]

[For medicines available only on prescription:]
<**Read all of this leaflet carefully before you start <taking> <using> this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your <doctor> <,> <or> <pharmacist> <or nurse>.
<- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.> [Do not include this statement in case of hospital use.]
- 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.>

[For medicinal products subject to additional monitoring ONLY: The black symbol and the explanatory statement should appear as a fifth point on this list, in which case the black symbol would replace the dash]
<{Black symbol} This product is subject to additional monitoring for rapid identification of safety information.>

[For medicines available without a prescription:]
<**Read all of this leaflet carefully before you start <taking> <using> this medicine because it contains important information for you.**
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.
- 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 must talk to a doctor if you do not feel better or if you feel worse <after {number of} days>.> “

[For medicinal products subject to additional monitoring ONLY: The black symbol and the explanatory statement should appear as a fifth point on this list, in which case the black symbol would replace the dash]

<{Black symbol} This product is subject to additional monitoring for rapid identification of safety information.>

Although the black symbol is currently a legal requirement under the new pharmacovigilance legislation published in Directive 2010/84/EU, we retain concerns about using this symbol in package inserts. To begin with, this symbol will raise strong mistrust in patients using medicines that have been insufficiently investigated and patients will feel that they are being used as guinea pigs in an effort to discover what side effects the medicine might cause.

Secondly, many medicines have a shelf life of up to 5 years. Where it has been assessed that the black symbol is no longer required for a particular medicine - and the relevant company had just previously produced and sold a new batch - patients will receive a medicine with a package insert containing wrong information for up to 5 years. In addition, patients could be confused given a situation where previously they had used the same medicine with a newer package insert; then to find in a later package insert the advice that the product is “subject to additional monitoring.”

Both aspects provided clearly illustrate that the black symbol and its explanation are inappropriate in the proposed format for the package insert - printed and contained in the medicine box. Nowadays of course, rapid amendments are possible using electronic files delivered via the internet; however, this cannot work effectively without recall of all previously dispatched but unsold batches carrying the black symbol on their package insert - in a case where the symbol has been deemed to be no longer required. Therefore, we propose a discussion relating to the deletion of the black symbol and its explanatory statement from the package insert.

3 Amendments relating to encouraging reporting of side effects

3.1 SmPC amendments concerning reporting of side effects

The QRD template draft provides the following new text relating to the SmPC chapter 4.8, which can be assessed as acceptable.

“**4.8 Undesirable effects**

<Paediatric population>

[For ALL medicinal products:
The new sub-heading should appear at the end of the section 4.8]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported via {insert information on the relevant 'national reporting system' – *details will be defined at national level*}. "

3.2 Package insert amendments concerning reporting of side effects

The QRD template draft provides the following revisions in package insert chapter 4:

"**4. Possible side effects**

<Additional side effects in children <and adolescents>>

[For ALL medicinal products:
The new sub-heading should appear at the end of the section 4]

Reporting of side effects
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' - *details will be defined at national level*} or you can report via {insert alternative ways of reporting – *details will be defined at national level*}. By reporting side effects you can help provide more information on the safety of this medicine."

We must voice our concerns at the possibility of laymen reporting side effects, such as via internet, without assistance by healthcare professionals because separation between side effects of a medicine and effects caused by the individual diseases, 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 weak data and huge difficulties are expected in the implementation process of these data in future product information of such as SmPC and package inserts.
Furthermore, a package insert is created to inform patients. Using package inserts for other aspects, such as increasing the number of side effect reports, deflects from the key intention to inform patients about the correct use of medicines.

However, the new legislation demands a statement in package inserts relating to reporting of side effects; therefore, only a very short addition should be included in the QRD template in which, preferably, only one nationally contact is provided. Any reference to national differences is irrelevant to patients and the intention to report side effects and should be deleted.
Therefore, we recommend the following amendment of the QRD template draft up a change of this legal requirement is considered:

"[For ALL medicinal products:

The new sub-heading should appear at the end of the section 4.]

Reporting of side effects

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: {insert the relevant 'national reporting contact details}."

4 Further required QRD template amendments

Apart the intended QRD template revisions described in chapters 2 and 3 of this statement, we recommend the following three very essential amendments based upon the results of package insert tests and current legislation:

Contraindication section of the SmPC

The SmPC wording of the current QRD template is:

"<Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 <or {name of the residue(s)}>.>"

The package insert wording is:

"<if you are allergic to {active substance(s)} or any of the other ingredients of this medicine (listed in section 6).>"

A hypersensitivity, such as relating to lactose is not always an allergy and is not generally a contraindication for using a medicine. According to Directive 2001/83/EC, article 59, the package insert must be in accordance with the SmPC [10]. Therefore, we recommend replacing the word "hypersensitivity" in the SmPC text with "allergy", as follows:

"<Allergy to the active substance(s) or to any of the excipients listed in section 6.1 <or {name of the residue(s)}>.>"

Pregnancy and breast-feeding section of the package insert

The QRD template sentence of this section is:

<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.>

Readability tests showed significant comprehensibility problems with this QRD template sentence where the medicine is contraindicated for pregnant or breast-feeding women, as the last part of this sentence "… before taking this medicine" implies that the medicine can be used during pregnancy and breast-feeding; however, this is not allowed if a contraindication

exists. Therefore, we recommend replacing the word “this” with the more general “any” so that the future QRD template sentence reads:

<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 any medicine.>

Side effect frequency explanation used for package inserts

The wording for 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 QRD template intended for package inserts, which is closed on one side only, e.g. “common, may affect up to 1 in 10 people”. Again, this conflicts with the Directive 2001/83/EC, article 59, as here the package insert is not in line with the SmPC.

Therefore, we recommend using the side effect frequency explanations as published by the EMA in 2007, e.g. “common, affects 1 to 10 users in 100” as this form is in compliance with the frequency explanation recommended for the SmPC [8, 11]. Furthermore, the EMA side effect frequency explanations published in 2007 were successfully tested in two readability test studies - one with 1105 participants investigating 10 package inserts and another with 5091 participants investigating 295 package inserts. The results 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 [7, 12, 13].

4 Conclusion

According to the explanations provided in this statement, the black symbol should continue to be provided, together with its explanatory statement, until the relevant legal requirements have been amended; however, it must not be used in front of the medicine name. Newly inserted QRD template texts must be as short as possible and any texts either not in compliance, or not essential to fulfil current legislative obligations, should be amended or deleted.

This statement was prepared by:

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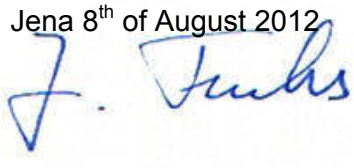
Signature: 

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