What's wrong with the QRD-template?

This review lists 271 comments on the QRD-template.

Not for publication.

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1. Scope of this review

This review set out to investigate and describe the problems with the QRD-template version 7.2 (October 2006).

The review was instigated by a question of a representative of a Regulatory Authority during a conference in Brussels in September 2007. He asked: 'What is wrong with the template?'.

The Regulatory Authorities receive the test reports of successful Readability tests. These reports rarely mention the comments that test participants make about the standardized texts in the template. These reports do not provide feedback about the process of writing, designing and testing either. This review looks specifically at these points.

The comments are based on the aggregated results of a few thousand individual interviews during readability tests in different countries, in different languages for different types of medicines. This text has been circulated among colleagues and substantial improvements were suggested by Jane Teather and David Sless.

2. Approach

The question 'what is wrong with the template' needs to be approached in two steps:

Step 1. To discuss the phrases in the QRD-template and the directly related guidelines.

> The discussion of the individual phrases is presented in appendix 1. The clustering of the comments is presented in appendix 2. A summary of the results is provided in section 3.

Step 2. To discuss the role of the QRD-template in document development processes.

> This is presented in section 4.

The contents of this review is as follows:

3. Step 1. Comments on the QRD-template

3.1 List the comments and group these into clusters

The first activity was to list all the comments about the text in the QRD-template. The list is presented in appendix 1. The list contains 271 comments.

The comments are clustered into categories. The comments are clustered according to the activities of Marketing Authorization Holders. There are three main groups of comments:

1. Comments related to the development of Package leaflets: writing, designing and testing
   These comments are related to the text of the template, the use of visual variables and the reactions of readability test participants.

2. Comments related to the combinations of the Regulations, guidelines and other guidance
   These comments are related to a comparison of advice and legislation.

3. Comments related to instructions for the Marketing Authorization Holder.
   These comments are related to a the application of the instructions in the template.

Each of these three groups is further subdivided. An overview of all comments is presented in the table on the next page. A description of each group and subdivion, an example and the consequences are indicated in appendix 2.

The number of comments in each category is as follows:

1 - Comments related to the development of package leaflets		
a. writing		**85**
1 - too many words	30	
2 - incorrect use of words	20	
3 - inconsistent spelling	9	
4 - not enough information	8	
5 - provoking the wrong emotion	8	
6 - awkward use of English	5	
7 - inconsistent use of words	5	
b. designing		**48**
1 - inconsistent use of punctuation	11	
2 - inconsistent use of line breaks and indentations	9	
3 - inconsistent use of bold type	6	
4 - inconsistent use of linespace	6	
5 - inconsistent use of wordspaces	6	
6 - confusing use of punctuation	4	
7 - inconsistent use of bulleted listst	3	
8 - inconsistent use of capitals	2	
9 - inconsistent use of centered type	1	
c. testing		**76**
1 - questionable location	14	
2 - instruction cannot be followed	14	
3 - instruction not applicable in context	11	
4 - information does not match the expectations	9	
5 - instruction is unclear	7	
6 - instructions are conflicting	4	
7 - effect of the action is not beneficial	4	
8 - instructions are mentioned in different locations	4	
9 - instructions are incomplete	4	
10- reactions are in conflict with the Directive	3	
11- there are better alternatives	2	
2 - Comments related to conflicts with legislation and guidance:		**54**
a. Directive		
1 - Article 63,2 and 59	28	
2 - Sequence	7	
3 - Ignoring the Directive	1	
b. Guidelines	14	
c. EMEA-guidance	4	
3 - Comments related to the instructions for MAHs.		**8**
Total		**271**

3.2 Conclusions of step 1

The table on the previous page shows that there are substantial numbers of problems in each of the categories. The following conclusions can be drawn:

1. The text of the QRD-template is far from optimal. The template contains unhelpfully obscure language, uses too many words, and spells words inconsistently.

2. The design of the QRD-template is seriously flawed. Most visual variables – punctuation, bold type, indentation, wordspace and linespace – are used inconsistently. Furthermore, the template does not use visual variables to clarify the structure of the contents.

3. Asking participants in a Readability test about the text and design of the template shows that some texts and visual presentation are almost always questioned. Each readability test shows the same problematic issues.

4. The QRD-template is frequently in direct conflict with Directive 2004/27/EC, the Readability guideline, or any of the other guidelines of the EMEA and National authorities. This causes serious problems in the development of package leaflets, because it is unclear which documents prevail.

5. The instructions in the QRD-template for Marketing Authorization Holders are confusing and unclear.

Please note that this is not a quantitative list. There is no indication of the severity of the consequences of each comment, nor of the consequences of a category of comments.

Each of these 5 conclusions on its own is sufficient to warrant a serious reconsideration on the use of the QRD-template. The combination of these 5 conclusions makes it very hard to support the template in practice.

4. Step 2. The role of the QRD-template in the development process

This section provides 13 statements on the application of the template in practice.

There are three categories:
- Issues related to the usability of the information for the users.
- Issues related to the available guidance
- Issues related to the 'information development process'.

These statements are based on the observation of Marketing Authorization Holders when they apply the QRD-template in practice.

4.1 The usability of the information for the users

The European Directive 2004/27/EC states in article 63,2 that *'The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals'.* The results of Readability testing and research indicates that this is not achieved to a satisfactory level. There is a direct conflict between 'standardization according to a template' and 'providing information that enables the users to act appropriately'.

Statement 1. The template does not differentiate
The template does not vary according to type of medicine (POM or OTC, parenteral or self-administration), users (patients, nurses, pharmacists, doctors), actions (take, identify, decide, remember, react, ...), contexts (home, hospital, emergency, sport, ...) or language (22 EU-languages). A single template to cover a large variation of practical situations inevitable reduces the appropriateness in specific situations.

The template disregards the idea that different people require different formats which match their personal cognitive style. These differences must be taken into account if appropriate information needs to be provided. A single rigid template obstructs the provision of information in appropriate formats.

Statement 2. Standardized information is less likely to be read
The use of a single template for all medicines results in package leaflets that look and feel similar. Patients who use several medicines at the same time, and use medicines for a longer period will therefore receive many similar looking package leaflets. This makes is likely that package leaflets are ignored, even though they might contain new and relevant information. Even if the information in a package leaflet is optimally clear, understandable, applicable, relevant and suitable, it becomes less likely to be noticed if it is presented in a format that is difficult to distinguish. The template does not allow for alternatives to focus the attention of patient to modified information.

4.2 Available guidance

The EMEA website states that *'The templates are intended to provide applicants with practical advice on how to draw up the product information, ...'* and *'Provide useful guidance as to the content of the information to be supplied'.* The following statements are based on an analysis of the practical application of the template. Both the phrases 'practical advice' and 'useful guidance' can not be verified in practice.

Statement 3. The template does not help applicants
The EMEA website states: '*The information contained in these documents is nonexhaustive; applicants should also refer to all relevant EU legislation and guidelines when drawing up their application. It is the applicant's responsibility to ensure that the product information complies with all such requirements.*' This statements diminishes the practical value of the template for applicants. Using the template does not guarantee that product information is compliant. In practice, each applicant must compare the templates with all other documents. There is no guidance which of these two document should prevail. If applicants really need to consult all other documents anyway, then the template just adds another level in the process.

Statement 4. The template does not help the writing of package leaflets.
The template must be used as a starting point for the development of a text for a package leaflet. Each author needs to consider the text to make sure that it 'enables people to act appropriately'. It is very likely that the standardized texts in the template are not absolutely suitable for each individual medicine. It is therefore likely that an author will suggest changes of the standardized texts.

It is unclear which modifications of the text of the template would be acceptable in the registration process. The pressures on Marketing Authorization Holders lead to follow the safest road and follow the text of the template exactly. This results in a continuous repetition of the same problematic issues. It also requires substantial efforts to 'work around the template' to write texts that are suitable.

Statement 5. The template does not help the designing of package leaflets.
The template must be used as a starting point for the visual design. It provides the general structure and sequence and provides many typographical specificiations. Each designer is confronted with the internal and external inconsistencies. It is likely that a designer will suggest changes of the visual design.

It is unclear which modifications of the design of the template would be acceptable in the registration process. The pressures on Marketing Authorization Holders lead to follow the safest road and follow the design of the template. This results in a continuous repetition of the same problematic issues.

Statement 6. The template does not help the testing of package leaflets.
Each Readability test reveals many similar issues. These are caused by the standardized text and design of the template. The template forces on Marketing Authorization Holders to make the same known mistakes again. This wastes the time and energy of both test participants as well as interviewers. This practice seriously reduces the value of a diagnostic test.

Statement 7. The template does not follow 'best practice'
The EMEA website states that the QRD templates *'Define the format and layout for summary of product characteristics (SPC); labelling and package leaflet'.* Although there is clear guidance on the format and layout in which the documents must be submitted to the EMEA, there is very little guidance on the format and layout in which information must be presented to 'users' (patients, pharmacists, doctors, nurses, ...). The format and layout of the template are inappropriate for those users. The template itself, and its translations, should be a good example of best practice.

Statement 8. Instructions must be tested
The EMEA website states: *'The templates are intended to provide applicants with practical advice on how to draw up the product information, ...'* and *'Provide useful guidance as to the content of the information to be supplied'.* However, just like the legal obligation to test package leaflets to establish if they really 'enable users to act appropriately', it would be beneficial if the EMEA and

EU-guidelines would be tested to determine if they 'enable applicants to submit appropriately'. In other words, it would be beneficial to find out if the instructions really 'provide practical advice' and 'provide useful guidance' before these claims are made. Providing untested guidance is like supplying untested medicines. It might do more harm than good.

4.3 An information development process.

The template focuses on the information required by the EU-Directive. It provides specific guidelines for different types of information on the package leaflet, outer packaging and inner packaging. This approach has several consequences.

Statement 9. The template stifles developments
Both the development of new package leaflets, and the development of new approaches to provide users with appropriate information are hampered by the current template. It is unlikely that any novel approach would be tried in Europe. Each deviation from the template might delay the registration process and it is therefore not attempted.

Developments using digital technology, in combination with the supply of information in different modes, cannot be considered with the current template.

Statement 10. The template implies that information can be developed without users
Using the template and writing a text is only a very small part of the development process of suitable information. The real value of information can only be established by actual users in context. Involving users before (observation), during (diagnostic tests) an afterwards (evaluation) are essential to measure the quality of information and prove that modifications are real improvements.

The template is not integrated into an 'information development process', and it does not provide any guidance or references to such a process.

Statement 11. The template implies that package leaflets can be developed on their own
People do not use package leaflets on their own. Package leaflets are used in combination with other information, such as the information appearing on the medicine itself, and information on the outer packaging. The use of these three sources depends on the context. The template does not consider the combination of these sources.

It's necessary to consider that users will consult several sources simultaneously, and ignore others. Interviewing users will not only reveal issues related to package inserts, but also issues related to the combination of package leaflet, medicine pack and outer packaging. The template needs to allow for this. It is hard to understand why only the package leaflet needs to be tested, and not the outer packaging or the combination of all information.

Statement 12. The digital formats of the QRD-template are problematic
The use Microsoft Word as the prefered format of the template needs to be questioned. This software is not the most suitable for handling complex structured documents in different languages. The use of non-proprietary formats is preferable and needs to be considered.

The use of XML in the PIM-programme offers a suitable and promising development. However, the PIM-system makes it impossible to modify the texts of the QRD-templates. As a consequence, this programme will solidify the problems mentioned in appendix 1 for many years to come.

Statement 13: The experience that is gained through the readability test is not used.
The results of Readability tests that have been done in the last years have not had much influence on the text or the design of the template itself. The evidence has not been integrated into the template.

During the development of a text for a package leaflet, it is necessary to compare the texts of approved leaflets. Unfortunately, it is not known if these approved leaflets have been tested and what the results of these tests were. It is obligatory to test identical texts again, which is likely to result in very similar outcomes. Any real development is hampered because the test reports are not publicly available.

4.4 Concluding step 2

The grouping of these statements indicate that:

1. The current template is not user-centered. The differences between people, medicines, contexts and languages are ignored. A single template cannot provide a reliable basis for the provision of information to people.
2. The guidance is insufficient, incomplete, unclear and frequently conflicting. The available guidance does not optimally help Marketing Authorization Holders to write, design and test package leaflets.
3. The process that is implied is not very helpful. It stifles any development and it starts from the assumption that package leaflets can be developed independent of other information. The digital opportunities for document developments are to a very large extend unused.

Each of these 13 statements on its own is sufficient to warrant a serious reconsideration on the use of the QRD-template. The combination of these 13 statements makes it very hard to maintain any support the template in practice.

5. Conclusions of this review

The findings of step 1 and step 2 show that the current version of the template is highly problematic. It is not very useful as an example nor as a process.

- The 271 comments indicate that the QRD-template cannot accommodate the varied needs of different groups of patients.
    1. The text of the QRD-template is far from optimal.
    2. The design of the QRD-template is seriously flawed.
    3. Readability tests show that several issues are always problematic.
    4. The QRD-template is in at least 54 occasions in irreconcilable conflict with Directive 2004/27/EC, the Readability guideline, or any of the other guidelines of the EMEA.
    5. The instructions in the QRD-template for Marketing Authorization Holders are confusing and unclear.

- The 13 statements indicate that the QRD-template fits poortly into the document development processes of Marketing Authorization holders.
    1. The current template is not user-centered. It ignores different types of users, different types of medicines, different contexts and different languages.
    2. The guidance is insufficient, incomplete, unclear and frequently conflicting
    3. The implied process is not very helpful. It separates package leaflets from other information sources. It does not optimally use digital technologies.

The European Directive 2004/27/EC states in article 63,2 that *'The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals'.*

This review concludes that the use of the QRD-template is irreconcilable with the legal requirements of article 63,2 of Directive 2004/27/EC.

6. The consequences of the current approach.

The consequences of this approach for the main stakeholders are:

Patients
The consequence of the decision to adhere to article 59 and the use of a standardized template is that all medicines in Europe will have a comparable package leaflet. Unfortunately, these standardized leaflets are not optimal in most situations. The leaflets are likely to be ignored and patients search for more suitable alternatives, for example on the internet.

Pharmaceutical industry
The pharmaceutical industry has to spend an extraordinary amount of time to 'write around the template' and to 'redesign around the template'. The problems in the template need to be alleviated in each individual leaflet.

The Readability test has becomes a fairly futile activity. The results mainly confirm the standard problems in the QRD-template. Deviations from the template are not accepted and the comments of test participants are ignored in order to follow to template.

The conflicts in regulations and guidelines lead to uncertainty and unnecessary time investments. In most situations, it leads to frustration.

Regulatory authorities
The problems and conflicts are certainly noticed by the Regulatory authorities. The poor guidelines and conflicts in regulations lead here to frustration too. The current guidelines are poorly suited to check if information about medicines is suitable.

Continuous negotiations are necessary to discuss the discrepancies, to try to make decisions and communicate these univocally across Europe. The opinions of different rapporteurs vary substantially.

Pharmacists and doctors
At the moment, the knowledge and experience of pharmacists and doctors is to a very large extend ignored. Although they have a substantial knowledge of patients in particular circumstances, they are not involved in the provision of written information to patients.

Other considerations
The origin of the Directive and Guidelines within the Department of Enterprise and industry might have had a substantial influence on the perspective of the provision of information about medicines. Other perspectives, such as those based on environmental, financial, or public health might need to be considered too.

7. Requirements for an alternative approach

The conclusions of this review in section 6 and the consequences as they are described in section 7 indicate that it is might be beneficial to consider alternative approaches. This section describes the requirements for such an approach.

An alternative approach must start from the assumption that it is not possible to modify EU-directive 2004/27/EC. Although some of the comments in appendix 1 show serious flaws in article 59, it is unlikely that this Directive will be modified again soon. It is therefore essential to take Directive 2004/27/EC as the basis.

The conclusions of the review, as they are presented in section 4.2 can be rephrased as starting points for such an alternative approach.

Start from the perspective of users.

1. Make it possible to differentiate information according to the needs of different users in different circumstances.
2. Make it possible to differentiate information according to its relevance for people in specific contexts.

Develop suitable guidance

3. Support applicants and authorities by giving clear and coordinated step-by-step guidance.
4. Support writers in the development of texts.
5. Support designers in the development of a visual presentation of information.
6. Support testers in the testing process.
8. Show best practice.
8. Test all guidance beforehand.

Develop a suitable process

9. Support new developments and innovation
10. Integrate a package leaflet into a ‘information development process’
11. Consider the package leaflet together with other types of documents
12. Suggest, develop, test and use suitable digital formats
13. Learn from the test results. Make test results publicly available.

8. Recommendations: The next steps

The following five steps should be taken to develop information for patients that is 'full and comprehensible', 'clear, understandable and easy to use', and 'enables the user to act appropriately'.

1. Shift the emphasis from article 59 to article 63,2
The emphasis needs to shift to a stricter application of article 63,2. This article states that '*package leaflets must enable the users to use medicines appropriately'*. The information elements and sequence of article 59 will still be used, but the main aim of the provision of leaflets must change from 'internationally standardized' to 'suitable for individual patients'.

2. Investigate 'users', 'actions', and 'appropriate'.
If article 63.2 is used as a basis, then it is necessary to apply a process that investigates 'users', 'actions' and 'appropriately'. For every medicine it is essential to find out how it needs to be handled and by whom. Medicines are always used in a specific situation and this situation must be taken into account. The list of 'users' and 'actions' is the starting point. It is necessary to establish for each action how important it is and what the risks are.

3. Develop guidance that helps industry and authorities.
It is necessary to develop guidance that supports both industry and competent authorities. Guidance should help both industry and authorities to develop and control the quality of information about medicines for people.

4. Develop processes that helps industry and authorities.
It is necessary to develop processes that supports both industry and competent authorities. The integration of 'document development processes' within an 'information strategy' needs to be initiated and developed.

5. Education and training
Before the first four points can be introduced, it is necessary to understand the fundamental concepts of providing information to people. Without a basic knowledge of the essentials of information design, it is likely that the same mistakes will be made again.

It is fairly easy to start these five activities immediately.

Appendix 1: A line by line commentary.

The colour coding:

Yellow: These texts are mentioned in the QRD-Template (version 7.2, October 2006)
The QRD-template: Version 7.2, 10/2006

Blue: These texts are mentioned in the The annotated template (Version 7.2, October 2006)
The annotated template: Version 7.2, 10/2006

Line 1: **PACKAGE LEAFLET: INFORMATION FOR THE USER.**
[Heading to be printed].

Comments about line 1:

a. *Package leaflet*. This is not the common word for patients to refer to this type of information. A common word would be 'insert'.
b. Package *leaflet*. It might not be a leaflet but a booklet. Other formats are possible too.
c. *Package leaflet*. It is very uncommon to indicate the 'genre'. People easily recognize that it is a 'package leaflet'. (The box does not have to mention 'outer packaging', nor does a blister mention 'inner packaging'.)
d. 'Information for the user': It is fairly clear that the leaflet presents 'information'.
e. 'Information for the user': 'User' is not the most suitable descriptor to address readers of package leaflets. It suggests that there are other types of information available that is not given to patients.
f. 'Information for the user' is inappropriate for products where there is a difference between the patient and the person who administers a medicine. Not only 'professional healthcare providers' but also family, parents and other carers.
g. The visual presentation of this heading is inapproapriate. The use of all capitals, bold and centered type should not to be copied in the mock-up. The Draft readability guideline states: "The widespread use of capitals should be avoided (Chapter 1, section A, point 1, third bullet.). It suggests that 'Capitals may be useful for emphasis.' In a package leaflet, Line 1 does not need to be emphasised. The use of capitals in the template is in conflict with the guidance in the EU-Draft Guideline.
h. The annotated template states: *[Heading to be printed]*. This is confusing, because it is suggests that other headings do not have to be printed.
i. The word 'heading' refers to different typographical items. The 'heading' of the leaflet, the 'headings of the chapters', and the 'headings of items'. For patients these must be in a clear hierarchy to enable the 'scanning' of a leaflet. The Draft readability guideline states: *'Same level headings should appear consistently (numbering, bulleting, colour, indentation, font and size) to aid the reader.'* The QRD-template is in conflict with this guideline.

Note about Line 1:

1. The heading is likely to be the first sentence to be read, and it is a valuable opportunity to present relevant information and focus the attention of the reader. Stating 'Package leaflet: information for the user' as the first line is not the most effective and wastes the first few moments of attention of readers.

   This heading, whatever the exact words, is useful in the multi-part document submitted by the MAH. In the formatted leaflet, it is not only redundant, but a waste of space. It is clear from the context that what the user takes out of the packet is a leaflet (or booklet, or whatever). No such

title should be necessary; but, if a title is preferred, something like '**Information about your medicine**' would be appropriate for some medicines.

Line 2: **{(Invented) name strength pharmaceutical form}**

[The (invented) name of the medicinal product in the RMS (referred to as X throughout this document) followed by the strength and pharmaceutical form (i.e. as it appears in the SPC) 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.]

The introductory notes on page 16 of the Annotated Template states: 'Throughout the text "X" stands for the (invented) name of the medicinal product.'

Comments about line 2:

a. After these 2 notes, the second line still refers to '(invented) name' and not to 'X'. If the convention would be followed it should state {X strength pharmaceutical form}
b. There is no differentiation between these three very different parts of information. In most situations, this is not read as a sentence, but as a sequence of three units of information. It must be possible to separate these by adding typographic separators such as comma's, hyphens, or tildes.
c. It is not clear why this line must be stated in bold. That does not help users to identify the medicine.

Line 3: **{Active substance(s)}**

Comments about line 3:

a. The name of an active substance is for patients hard to remember or recognize. In the template, this information is presented without a context. It would be easier for patients if it states: 'Active substance: {active substance(s)}'.
b. The function of the '}' at the end of the first line, and the '{' at the beginning of the second line is unclear. These can be deleted. It is in conflict with the 'Compilation of QRD decisions on stylistic matters in product information' (February 2008) which states: 'Once a particular style or house style has been selected it must be used consistently throughout the text.'
c. This advice contradicts with the advice in the Draft Guideline. The Draft guideline states: 'Avoid repetition of information by cross-referring to information which is under another heading where this is appropriate.' The same information is mentioned in section 6, line 58.

Notes about Line 1-3.

1. The action that should be supported in the first lines of the package leaflet is the 'identification of the product' by users. The Directive states: 'for the identification of the medicinal product' (article 59, 1(a), (i)). A package leaflet must 'enable the users to act appropriately' (article 63, 2). 'Identification' is one of these actions. The template as it is at the moment does not 'enable the users to identify a medicine' in an optimal manner. There is no visual link with the medicine itself nor with the packaging. Most users do not identify their medicine according to the way this information is stated on the leaflet — they use the brand name and the **logotype**.

   It should be **mandatory** for the logotype, as used on the package, to appear on the leaflet (as well as on the blister pack, bottle etc.) — this would help prevent confusion between leaflets for people taking multiple medications. Although it will nearly always be impractical to reproduce the colours used on the package, the logotype on the leaflet should otherwise be visually identical. The main aim of this information is to enable the user to relate the package insert to a specific medicine (this leaflet is about those pills), and to enable the user to recognize the medicine (these pills look like this). This is not 'promotional' but only aids the identification of the medicine. If the package leaflet must 'enable the user to identify the medicine', then this must be monitored. 'Are medicines correctly identified by users and do we find that appropriate'? Otherwise, there is

a direct conflict with article 63,2.
2. The motivation for the use of centered type in the first three lines is not clear.

Line 4: **<Read all of this leaflet carefully before you start <taking> <using> this medicine.**

Comments about line 4:

a. 'carefully' is patronizing. It assumes that patients will be reading it in a 'careless' way. There is no evidence to suggest that.
b. 'all of this' is patronizing. It assumes that patients are not capable of finding the most relevant information themselves.
c. This instruction suggest that people must read the disposal instructions and the list of MAH-representatives before taking the first dose? In practice, it is unlikely that patients read a leaflet in sequential order from the first line to the last line.
d. In many situations, patients will never see the leaflet. For example in hospitals, care homes, and during operations. If the leaflet is only available after a medicine has been given, this obligatory phrase is not suitable.
e. If the package leaflet must 'enable the user to read the leaflet', then this must be monitored. 'How many leaflets are read by users and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2. Investigations into the 'reading' of leaflets (Raynor, University Leeds) have shown that substantial numbers of people read at least part of the leaflet. Most people are seem to be aware that a leaflet is available.
f. It is not clear why this sentence is presented in bold type. It is now presented as if it is a heading, but it does not fulfill the same purpose.
g. The annotated template mentions that line 9 to 14 are 'For medicinal products available without a prescription:'. A similar instruction for line 4 to 8 would be helpful.

Line 5: - Keep this leaflet. You may need to read it again.

Comments about line 5:

a. Some leaflets might take the form of a booklet.
b. It is not clear why there is a hyphen here. The guidelines – both the 1998 version as well as the 2006 draft – states that bullets are preferred. If there is no difference between bullets and hyphens, than this must be made clear.
c. 'Keeping a leaflet' is a user action that must be enabled by the package leaflet. The appropriate action is to 'keep the leaflet'. If the package leaflet must 'enable the user to keep the leaflet', then it must be monitored. 'How many leaflets are kept by users and do we find that appropriate'? Otherwise, there is a conflict with article 63,2.
d. The current variation formats, folding techniques and paper quality does not make this easy, and frequently is in direct conflict with Directive Article 63, 2. [We do not make it easy for patients to 'keep the leaflet'.]
e. 'Keeping' is impossible in hospitals and elderly care homes, where patients very rarely receive package leaflets.
f. It is likely that the leaflets for chronic medicines will be thrown away quicker than leaflets for temporary uses. The advice is therefore more appropriate to some medicines. Including this sentence in all medicines is not the most effective.
g. 'Re-reading a leaflet' is a user action that must be enabled by the package leaflet. The appropriate action is to 'read the leaflet again'. If the package leaflet must 'enable the user to keep the leaflet', then it must be monitored. 'How people read their leaflets again and do we find that appropriate'? Otherwise, there is a conflict with article 63,2. It might be more appropriate to state: 'you may need to refer to it again', or just 'you may need it again' to describe real-life scenarios.

Line 6: - If you have any further questions, ask your <doctor> <or> <pharmacist>.

Comments about line 6:

a. There is a slight conflict between this sentence and the final sentence of section 3. The final line of section 3 states: '<If you have any further questions on the use of this product, ask your <doctor> <or> <pharmacist>.>' There is a difference between 'any further questions' and 'on the use of this product'. It might be clearer to delete 'on the use of this product' at the end of section 3.
b. This sentence is in conflict with the statement at the end of section 6. Line 66 states: *'For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:'* In most package leaflets, people are referred to three different sources, of which the MAH is the first source. Further questions, that is, after the questions have been asked to the MAH, should be answered by a doctor or pharmacist. This is probably not what was intended. The doctor and pharmacist must be the first places to go.
c. 'Asking questions' is essential, but it can be questioned if this is the right place to mention that. It fits awkward within the EU-Directive structure that determines that the first part of the leaflet must be about the 'identification of the medicinal product'.
d. If the package leaflet must 'enable the user to ask questions', then this must be monitored. 'How many and which questions are asked by users and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
e. 'any further questions' sounds over-formal and artificial. 'any more questions' might be a suitable alternative.

Line 7: - <This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.>

Comments about line 7:

a. This starts from the idea that patients will pass medicines on to other people. It is the second time in 3 sentences that patients are warned in a patronizing way. 'Patients are so stupid that they give their medicines to others. We've got to warn them.'
b. If the package leaflet must 'enable the user not to pass medicines on to others', then this must be monitored. 'How many medicines are passed on and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
c. The word 'symptoms' might not be understood. 'Signs of illness' might be more appropriate in some circumstances.

Line 8: - 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>.>

Comments about line 8:

a. A common reaction is: 'Hold on, I've only got to here and they are allready talking about side effects. I don't even know what the medicine is for yet.' This is not the correct location to mention side effects. People cannot know what they are at this point in the leaflet. 'tell your doctor or pharmacist about side effects' is good advice, but it is here in the wrong place. Research (Wogalter, Adams) shows that instructions are most likely to be followed if they embedded in logical sequential series. Information about side effects must therefore be in section 4 of the package leaflet.
b. There is a double space between 'If' and 'any'. Please delete. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (Version 11, February 2008) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. The use of a double wordspace is in conflict with this QRD decision.

c. Awkward English: the plural of 'side effects' conflicts with the singular form of 'gets'. In every interview, every native English speakers stumbles here. After re-reading it is either confirmed to be correct English – 'any' is singular – or a remark is made that it should be 'get' and not 'gets'.
d. For a patient, any side effect is serious. Patients should be encouraged to discuss any worry they have with their doctor. Leaving the interpretation of 'serious' to a patient might not be appropriate in all circumstances. Sometimes, 'less serious' effects might be symptoms of very severe side effects.
e. If the package leaflet must 'enable the user to tell about side effects', then this should be investigated. 'How many side effects are mentioned by users and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
f. 'Please' is nearly always redundant, and dilutes the message.

[Line 8 is repeated in Line 50. There are some more comments there.]

Note about Lines 4 to 8.

1. These five lines tell the reader to: 'read the leaflet, keep the leaflet, ask questions, do not pass the medicine on, tell your doctor or pharmacist about side effects'. These instructions are strongly dependent on the context in which a specific medicine is used. The inclusion of these texts must be based on research findings and evidence that it is necessary to include them. Otherwise, they are unlikely to 'enable the user to act appropriately'.
2. It is not clear if this list of three or four items can be seen as a 'list of bullet points' as it is mentioned in the Draft Readability guideline. However, the visual style diverges from the Draft Readability Guidance. There is no guidance on lists.

[For medicinal products available without a prescription:]

Line 9: **<Read all of this leaflet carefully because it contains important information for you.**

Comments about line 9:

a. The phrase 'important information for you' is found patronizing. A patient can decide this for himself/herself.
b. The relevance of this sentence in a patient leaflet can be questioned.
   - The instruction 'Read' is superfluous – it is the only thing that people can do with written information.
   - 'all' is paternalistic and suggests that patients are unable to make decisions what is relevant.
   - 'of this leaflet' can be deleted because the person is looking at the leaflet when this sentence is read. For some medicines, it would be useful to consider the context and refer the patient to the outer packaging too.
   - 'carefully' is unclear, because it is impossible to read 'carefully'. If there is a difference between 'careful reading' and 'other forms of reading' than this must be made clear.
   - 'because it contains important information' might be assumed to be correct. Otherwise the competent authorities and pharmaceutical industry are putting information in medicine boxes that is not important.
   - 'for you' is unnecessary. If a person finds a leaflet in a medicine pack that he/she has just purchased in a pharmacy, it is likely that the included leaflet is for the person who bought it. If it is purchased for a relative, it is incorrect.
c. If the package leaflet must 'enable the user to read the leaflet', then this must be monitored. 'How many leaflets are read by users and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

Line 10: This medicine is available without prescription. However, you still need to <take> <use> X carefully to get the best results from it.

Comments about line 10:

a. How can you take a medicine carefully? How can a patient check if a medicine is taken carefully? If a patient takes it without taking care, will the results be worse?
b. The word 'carefully' is used here in relation to 'taking' or 'using'. In Line 9, it is used in relation to 'reading'. It insults the reader by implying that he/she has an intention not to be careful.
c. The phrase 'However…still' is being used to imply that people will expect to be able to treat a non-prescription medicine frivolously. This seems patronising. Is there evidence that people assume there is no need to be careful unless a medicine requires a prescription? If it is important for patients to 'take medicines carefully', then it is also necessary to mention in the introductory information for 'prescription only medicines' that 'it is necessary to take medicines carefully'. However, it is a very unclear statement: how can a person take or use a medicine carefully? What are the exact actions and how do they differ from taking medicines in any other way?
d. The word 'still' only makes sense in the sequence of the text in the template. For medicines that are available without a prescription, 'still' does not refer directly to 'medicines that are available on a prescription only'.
e. If the package leaflet must 'enable the user to take medicines carefully', then that should be investigated. 'How many medicines are taken carefully and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

Line 11: - Keep this leaflet. You may need to read it again.

Comments about line 11:

See comments about line 5.

Line 12: - Ask your pharmacist if you need more information or advice.

Comments about line 12:

a. If the package leaflet must 'enable the user to ask a pharmacist for advice', then that should be monitored. 'How many and which questions are asked and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

Line 13: - You must contact a doctor if your symptoms worsen or do not improve <after {number of} days.>

Comments about line 13:

a. The full stop must be after the guillemet: '>.' Otherwise, this line could end without a full stop. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, Version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. Not using a full stop in this sentence is in conflict with this QRD decision.
b. The words 'You must' are redundant. Simply 'Contact a doctor' more direct.
c. 'worsen' is a very obscure word in English, and many people will not recognise it — 'get worse' is normal usage.
d. '… symptoms worsen or do not improve'. It is suggested that 'symptoms must improve' after a patient takes an OTC-medicine. This has been misinterpreted as 'increase' and not as 'remain the same'.
e. If the package leaflet must 'enable the user to contact a doctor if symptoms continue', then that should be monitored. 'How often do users contact a doctor and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

Line 14: - 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>.>

Comments about line 14:
See comments about Line 8 and Line 50.

Line 15: **In this leaflet:**

Comments about line 15:
a. It is not clear why this line is presented in bold, and if it is necessary to copy this typographic style into the design of the package leaflet.
b. It is not clear why there is a colon ':' at the end of this line. It can be deleted.
c. The visual presentation suggests that this is a 'bulleted list' according to the Draft Readability Guideline. However, the numbered items that follow this list are in conflict with this advice.

Line 16: **1. What X is and what it is used for**

Comments about line 16:
a. This title frequently confuses people. For patients, X is a medicine. The question 'What X is' is not the most important question for most patients. 'What it is used for' is more important.
b. The sequence of the two questions is therefore in conflict with the 'easy to use' requirement of article 59,3. The title would be easier to use if it followed the sequence of relevance for patients. The Directive makes this possible. It clearly separates the pharmaco-therapeutic indications and the therapeutic indications. The template brings them together into a single section.

Line 17: **2. Before you <take> <use> X**

Comments about line 17:
a. For prescription only medicines that are taken at home, this information comes too late. It should have been discussed with the prescribing doctor or with the pharmacist. A patient can only see the leaflet after they've arrived at home. The practical value of this section is in that particular context more like a checklist. For medicines that are used in other contexts, this information is very rarely seen by patients.
b. For OTC-medicines, this information is not available at the point of purchase. It is usually not possible to open a package to read the leaflet in a pharmacy or chemist. For medicines that are used in hospitals or during operations, this information is irrelevant to a patient. Including this statement in the package leaflet might not be the most appropriate in all circumstances. If it is necessary 'to enable the user to act appropriately', it might be necessary to consider other locations for this vital information.
c. This phrasing frequently confuses people when a medicine is administered by a health professional. It suggests that the patient has to act. For infusion medicines, that is not the case. Once a patient has the incorrect idea that they have to do something themselves, the rest of the package leaflet does not make much sense until they revise their assumption. When a patient reads on, it only appears in section 3 that an incorrrect assumption was made. This is detrimental for the confidence that patients have in the quality of the information.

Line 18: 3. How to <take> <use> X

Comments about line 18:
a. For medicines that are administered by a healthcare professional, this heading is difficult to understand for patients. It suggests that the patient must be actively 'taking X' or 'using X'. This

might not be the case for medicines administered in hospitals, elderly homes or during emergencies.

Line 19: 4. Possible side effects

Comments about line 19:
None

Line 20: 5. How to store X

Comments about line 20:
a. In the template, this line is the only one in this list that is marked as a bulleted list in the Microsoft Word-software. The other five headings use a tab. It is unclear why this difference is made.
b. This phrasing frequently confuses people when a medicine is stored in a hospital. It suggests that patients have to store the medicine themselves. Once this incorrect assumption is made, the package leaflet becomes frequently very confusing. 'It is given to me in a hospital and I have to store it at home?'.

Line 21: 6. Further information

Comments about line 21:
a. The word 'further' is not correct in this heading. The information in this section does not provide 'further' information in the sense of 'more detailed' information. It provides 'other information' according to the categories of the Directive article 59.

Notes about Lines 1 to 21.
1. Some readability tests indicate that the contents list – line 15 to 21 – is appreciated. Interviewees commonly state that they like the contents list (though that is seldom what they call it), and that they perceived it as being useful during the interview. Many have said that this is the only leaflet they have seen that has a contents list — almost certainly not true.
   However, in practice, it is of very limited use, because of the structure of the leaflet. It includes only level 1 headings, and does not give people any guidance as to where they will find, for example, information about driving or pregnancy, or about what to do if someone takes too much. 'Before you take X' is not a useful signpost, as they don't expect that information to be under that heading anyway.
   In leaflets where space permits, it would be useful to include level 2 headings in the contents list (with the hierarchy clearly indicated using typography, spacing, indents etc, as appropriate). When a leaflet takes the form of a booklet, this is more important (and many booklets would also benefit from an alphabetical index).

2. However, another common reaction is that these 17 lines are too long. 'I've reached here and there has not been anything that is of interest to me.' is a fairly common remark.

3. Line 1 to line 3 correspond with article 59, 1(a), (i). In the Directive, this section is about the 'identification' of the medicine. The information that must follow Line 22 follows the article 59, 1(a), (ii) describes 'the pharmaco-therapeutic group or type of activity'. These two articles have the intention to 'identify the medicinal product'.
   The sentences in lines 4 to 8, 9 to 14, 15 to 21, and line 22 do not have this intention. They are not there to 'identify' the product. However, they appear *in between* the required information to 'identify the medicinal product'. These additional lines make it for most medicines more difficult for users to identify a medicine.

4. The comments of Readability test participants seem to imply that it would be worth investigating if this space could not be better used to – for some products only – mention the 'most important points'. These could be the main points that a user must know about a specific medicine. The current points are applicable to all medicines. It might be more beneficial to make them specifically applicable to a single product.

Notes about Lines 16 to 21.

1. It is not clear why the right indentation of this sentences is put as – 0,05 cm. Most other sentences do not have a right indentation.
2. The contents list in line 16 to 21 is likely to be sufficient if the package leaflet takes the form of a broadsheet. If the package leaflet takes the form of a small booklet, it is unlikely that the contents list is sufficient. If people need to find information in a booklet, than it must be possible to modify the contents list.

SECTION 1.

Line 22: 1. WHAT X IS AND WHAT IT IS USED FOR

[Pharmacotherapeutic group.]
[The pharmacotherapeutic group or type of activity should be stated here using patient understandable language.]

Comments about line 22:

a. There is a difference between Directive article 59, 1(a), (i) which states 'in terms easily comprehensible for the patient' and the text that appears in the annotated template: 'using patient understandable language'. If there is no difference, please use the same words.
b. The spelling of pharmaco-therapeutic is not consistent. There is a hyphen in the Directive which is omitted in the template. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. Inconsistent spelling is in conflict with this QRD decision.
c. The Directive states that this information is for 'identification purposes'. Patients are unlikely to use pharmacotherapeutic groups to identify their medicines. This highlights a conflict between article 59 and article 63 of the Directive. The information that must be provided according to article 59 does not 'enable the user to act appropriate' as it is stated in article 63.
d. The question in the heading does not cover the anticipated answer of patients. If you ask a patient 'What is X?' than it is very unlikely that a patient will refer to the pharmaco-therapeutic group. In most situations, patients will refer to what a medicine does.

[Therapeutic indications.]
[The therapeutic indications should be stated here, using patient understandable language.
If appropriate, specify that:]

Comments about line 22:

e. This information should describe why a particular medicine has been prescribed. This section could contain information about the situation that needs to be treated, a description how a medicine changes this situation, and a description of the desired outcomes. Additional information in this section does benefit patients (See: Vander Stichele, R., VanDierendonck, A., De Vooght, G., Reynvoet, B., Lammertyn, J. (2002) 'Impact of benefit messages in patient package inserts on subjective drug perception. *Drug Information Journal.* volume 26. 201-208.) and would be perfectly in line with article 62: *'The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of the product characteristics which is useful for the patient, to the exclusion of any element of a promotional nature.'* Unfortunately, this article 62 is ignored in the QRD-template.

Line 23: <This medicine is for diagnostic use only.>

Comments about line 23:

a. It is not clear why 'medicines for diagnostic use' are separated here. For patients, this statement does not help very much. If it is vital to make a special statement about this group of medicines, than there must be a motivation in the Annotated template.

SECTION 2.

Line 24: **2. BEFORE YOU <TAKE> <USE> X**

[Additional sub-headings within the headings given below may be included if needed to increase readability.]

Comments about line 24:

a. This heading is misleading and ambiguous. Presumably the intended meaning is 'Points to check before you start taking X', but people don't always interpret it that way. For example, it could be taken to mean 'before you take each dose' (e.g. don't eat); or 'before you use a device for the first time' (e.g. prime the inhaler). In addition, it contains a lot of information about behaviour that might be affected or need to be modified, or situations that might arise, **while** the person is taking X. People see this as irrational. If these subsections are moved to a new main section 'While you're taking X' (without otherwise substantially changing their order or structure), scores in diagnostic testing improved. However, this was not permitted by the regulator.
b. The annotated template suggest that it is possible to include 'additional sub-headings within the headings given below.' The template has two levels of headings at the moment. Additional sub-headings would create a third level of heading. This is in direct conflict with the advice in the Draft Readability Guideline. This guideline states: *'The use of multiple levels of headings should be considered carefully, as more than two levels may make it difficult for patients to find their way around the leaflet.'* Adding level 3 subheadings can work pretty well if the layout and typography is handled effectively to signal the hierarchy (and if the MAH style guidelines permit the information designer to do this).
c. The criterion differs from the criteria used in the Directive. The Directive asks for 'legible, clear and easy to use' (article 59,3), 'written and designed to be clear and understandable, enabling the users to act appropriately' (article 63 paragraph 2). In point 40 of Directive 2001/83, there is also: 'full and comprehensible information'. Together with the criteria from the template – increase readability – and from the Draft guideline – easy to find their way around the leaflet, it becomes very hard to choose relevant and appropriate criteria.
d. All the criteria that are mentioned under point b are very hard to use in practice. They cannot be measured or observed directly. Article 63 of Directive 2004/27 states that package leaflets 'must enable the user to act appropriately'. That is a perfectly executable law. In order to comply with this article, it is necessary to:
   - find out who the users are,
   - find out which actions need to be undertaken,
   - determine what 'appropriate' levels of success or failure are.

   Once these three factors have been determined, it is perfectly possible to establish accurately if a leaflet 'enables the user to act appropriately'.
e. The word 'Readability' in the annotated template is incorrect. 'Usability', 'comprehensibility' or 'ease of navigation' would be more appropriate.

[List of information necessary before taking the medicinal product.]

'[The whole section 2 must take into account the particular condition of certain categories of users, e.g. children and the elderly (specify the age range; for children see CHMP Note for Guidance on Clinical Investigation of Medicinal Products in Children (CPMP/EWP/462/95)); special patient populations, e.g. patients with renal or hepatic impairment.]'

Comments about line 24 (continued):

f. The Directive states: *'take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions);'* (article 59, 2). This differs from the guidance in the annotated template that is cited above.
   The main difference is that the pregnant or breast-feeding women are taken not mentioned in this

statement in the annotated template. The consequence of this is that the information about pregnancy and breast-feeding is only mentioned in the sections about pregnancy and breast-feeding, and not in the absolute contra-indications at the beginning of section 2.

From the annotated template: *[Contraindications.]*

Comments about line 24 (continued):

g. The spelling of the word 'contraindications' differs between the annotated template and the EU-Directive. There is a hyphen in the Directive which is omitted in this part of the template. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. Inconsistent spelling is in conflict with this QRD decision.

Line 25: **Do not <take> <use> X**

Comment about line 25:

a. It is not clear if this must be seen as a list of bullet points or not. There are some similarities, but there is a large discrepancy between the presentation of this list and the guidance in the Draft Readability Guideline. This Guideline states: *'A list of bullet points should be short and should be introduced with a colon, with a single full stop at the end of the list. The list should begin with the uncommon and specific case, and end with the common or general case, unless this is inappropriate for the product.'* If bullet points are essential, than this list should be presented as such. The presentation at the moment does not make clear what is expected.
b. [Two points about this guidance:
   1) Of course a short list is preferable; but the length will depend on the number of contra-indications listed in the SPC. It is not possible to just leave a few out to make this list shorter. So, as a guideline, this is meaningless.
   2) From users' point of view, it seems best (if possible) to start with the most probable conditions. If the first one or two bullets are not applicable, the rest of the list is likely to be skipped.]
c. When bullet points are conditional clauses, for example, 'if you are…', 'if you have…', each individual point should begin with 'if', rather than 'if:' being used in the introductory sentence. The current presentation suggests that people must continue reading from the title onwards. The visual presentation does not make this easy. Test-participants have to re-read the title and subsequent phrases several times to figure out what the intention is.
d. The phrase 'Do not take/use' is inappropriate for medicines that are used in hospitals. Patients get the incorrect suggestion that they need to do something.

Line 26: - <if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of X.>

Comments about line 26:

a. The positioning of this statement as the first one under the heading 'Do not use X' suggests that it is the most important one, or the statement that is applicable most frequently. This might not be the case for all medicines.
b. Put the left guillemet before the hyphen ('< -'), not afterwards ('- <'). Now every leaflet must include the hyphen.
c. The active substance is at this point in the leaflet is unlikely to be recognized to patients. Although it is mentioned in line 3, it is unlikely that people realize that this is the name of the active substance.
d. The other ingredients are mentioned in section 6. A reference here to section 6 would be very helpful. It is unlikely that people can find the list of 'other ingredients' without such a reference.
e. In most situations, and especially for new medicines, it is impossible for patients to know if they are allergic. For new medicines, this phrase does not make sense. If it is necessary to include this

point, perhaps it should say 'if you know you are allergic…'. This would not always apply to new medicines, but there maybe special cases.

f. The 'allergic reaction' is covered again under the subsection about potentially allergenic excipients, which makes it all the more confusing. This statement might be in the wrong location.
g. Patients commonly confuse allergic reactions with side-effects. It is likely that they look under side-effects when they want to find information about an allergic reaction. This is probably partly caused by the similarity in meaning of 'effect' and 'reaction'.
h. If the package leaflet must 'enable the user to detect an allergic reaction, then this must be monitored. 'How can we avoid that people use medicines if they are allergic to the active substance or other ingredients and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
i. The signs and symptoms of an allergic reaction must be described. Otherwise, it would not be possible for patients to detect. The current structure does not allow for this. The only place is in section '4 Possible side effects'. This is hardly appropriate because of the difference between an allergic reaction and a side effect.

Line 27: - <if ...>

Comments about line 27:

a. Please delete one space after 'if'. It is a double wordspace now. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. The use of a double wordspace is in conflict with this QRD decision.
b. Put the left guillemet before the hyphen ('< -'), not afterwards ('- <'). Now every leaflet must include the hyphen.

[Give information on absolute contraindications here in accordance with the SPC; this should be in patient understandable language and should be strictly limited to contraindications, including contraindications due to interactions with other medicinal products. Other precautions and special warnings should be made in the next section. Care must be taken to ensure that complex details are not omitted. It is not acceptable to state only the common or major contraindications. Belief that a patient cannot understand a contraindication is not a reason for omitting it.]

c. These are not the only real contra-indications: Pregnancy and breast-feeding are omitted here. Furthermore, there are two statements in section 5 that should be placed here too. Line 53 states: 'Do not use X after the expiry date …' and line 54 states: 'Do not use X if you notice {description of the visible signs of deterioration}. For patients, it is hard to see why these two 'Do not statements' do not appear in the section 'Do not use X'. Main point is that the importance of the contra-indications varies according to the context. Some might be vital at some point of use.
d. If the package leaflet must 'enable the user to avoid using/taking a medicine, then this must be monitored. 'How can we avoid that people use medicines if this medicine use is contra-indicated and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
e. A list of contra-indicated medicines here is likely to be confusing for patients. A leaflet will have several lists of medicinces:
   - contra-indicated medicines
   - warnings related to other medicines
   - interactions with other medicines.

   The appropriate action for patients in all situations is: 'make sure that you tell your doctor about all the medicines that you are using'. It is the responsibility of a prescribing doctor to ask the patient, and to consider all factors involved before he/she prescribes a medicine. Asking a participant in a readability test about a contra-indicated medicine always lead to the same answer:

'That is really for my doctor to decide. I don't have any idea what all these names mean'. However, not all doctors ask, and the leaflet must cover that eventuality (for example, a hospital doctor may prescribe without asking the patient what they have on prescription from their GP).

f. The practice of referring to 'active substances' and not to brand names is understandable from several points of view. However, this practice makes it very hard for patients to realize that brand names and active substances might refer to the same product. Patients know their medicines by (1) what the medicine is to treat; (2) what its brand name is; (3) its active ingredient. Most people know (1), some people know (2), and only a minority of people know (3). So the key point is to include the indication, for example:
• **ingredient-a** or **ingredient-b**, to treat **condition**

[Appropriate precautions for use; special warnings.]

Line 28: **Take special care with X**

Comments about line 28:

a. This instruction is unclear: it does not tell people what to do. How can users/ people/ patients 'take special care'? If package leaflets 'must enable the user to act appropriately', then this statement does not describe the action very well. It does not tell people 'how to act'.
b. The annotated template suggests to combine 'Appropriate precautions for use' and 'special warnings' under this heading. This is in direct conflict with article 59 of Directive 2004/27/EC. The Directive states that the 'Appropriate precautions for use' must be followed by the 'forms of interactions with other medicinal products and other forms of interactions'.
c. The difference between 'special care' and 'normal care' must be explained. The word 'special' can be deleted if such a difference does not exist.
d. The phrase 'Take special care' is inappropriate for medicines that are used in hospitals. Patients get the incorrect suggestion that they need to do something.

Line 29: - <if you ...>

Comments about line 29:

a. Put the left guillemet before the hyphen, not afterwards. Now every leaflet must include the hyphens. So: <- if you …>.

Line 30: - <when ...>

Comment about line 30:

a. Put the left guillemet before the hyphen, not afterwards. Now every leaflet must include the hyphens. So: <- when …>.

Line 31: - <Before treatment with X,…>

Comments about line 31:

a. It is unclear what could be stated in stead of the … . It makes it difficult to make a grammatically correct sentence when it starts with: 'Take special care with X • Before treatment with X, …'.
b. It is not clear why there needs to be a sentence starting with 'Before treatment with X' in a section that is called 'Before you <take><use> X'. Could it be deleted?
c. Add space between 'X,' and '…'. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g.

punctuation, symbols, spacing, redaction style etc. The inconsistent use of wordspaces is in conflict with this QRD decision.

d. Put the left guillemet before the hyphen, not afterwards. Now every leaflet must include the hyphens. So: <- Before treatment with X, …>.
e. It is not clear why 'Before' starts with a capital and 'if' and 'when' do not.

[Information in patient understandable language, special warnings and appropriate precautions for use should be provided here.]

Comments about line 31 (continued):

f. This advice is in conflict with Directive 2004/27/EC. At this point, the information that is required in section 59, 2(c), (iv) is placed before the information that is required in section 59, 2(c), (iii). This is in conflict with article 59,1 that states that the information must be given in a specific order. The information about 'special warnings' must appear after the 'forms of interaction'.
g. It is not clear where the criterion 'in patient understandable language' comes from. Article 63,2 states: 'The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in the official language or languages of the Member State in which the medicinal product is placed on the market.' The words 'in patient understandable language' do not appear in the Directive. Focussing on the language only ignores the visual presentation of the text.
h. The phrase in the annotated template is hard to understand. It suggests that 'Information in patient understandable language', 'special warnings' and 'appropriate precautions for use' are three different items that must appear in this section. Only two of those - 'special warnings' and 'appropriate precautions for use' – are mentioned in the Directive. The order of these two items must be reversed to follow the sequence of information elements of article 59 of the Directive.

Note about Lines 28 to 31.

1. It is not clear if this list is intended as a 'list of bullet points' as it is described in the Readability Guideline. There is a difference between hyphens and bullets, the capitalization of 'Before' and the lack of a colon seems to indicate that this is not a 'list of bullet points'.

[Interaction with other medicinal products.]

Line 32: **<Taking> <Using> other medicines**

[Describe the effects of other products on the product in question and vice versa. Reference should be made to the intensification/weakening and the extension/shortening of effects.]

Comments about line 32:

a. Some products rely heavily on the interaction with other medicines. HIV treatment is an example. In that case, it is very difficult to follow this advice.
b. This subheading does not follow the principle of putting key words first so that that users are more likely to spot them when scanning through the leaflet. The key term here is 'Other medicines', and 'taking' or 'using' are secondary. Evidence from diagnostic testing indicates that users find the information more readily if this reads: 'Other medicines and X'.
c. This information might not be appropriate for all patients and all products. It is unclear which actions of users are enabled by this information. This type of information is probably more suitable for a discussion between doctors and pharmacists. Some experienced patients – HIV, diabetes – are likely to know more details than a leaflet can ever give. This subsection can vary enormously in its complexity and implications, and the template needs inbuilt flexibility. For example, if the medicine is to be taken as a short course by someone otherwise reasonably healthy, this may be relatively straightforward. For people taking multiple medications long-term, it is impossible for a leaflet to give information to enable them reliably to work out the possible interactions for themselves— the only sound advice is for them to discuss this with a doctor, pharmacist or other medical professional. Exhaustive lists of possible interactions in the leaflet

may serve only to confuse them.

d. The leaflet must mention two lists of medicines. The first list are those that are contra-indicated. The second list are those that might interact. The action for the patient is identical: they must tell their doctor that they use any medicines. The reaction of the doctor might be different. He/she cannot prescribe contra-indicated medicines or he/she needs to adjust the dose and/or find alternatives. The difference between the two lists is frequently unclear to patients, especially if they have to look for one specific medicine. They need to look in two locations. This is in conflict with the 'easy to use' requirement of article 59,3 of Directive 2004/27/EC.

Line 33: <Please tell your <doctor> <or> <pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.>

Comments about line 33:

a. The word 'obtained' is misunderstood. It could probably be replaced by 'bought'.
b. The Draft readability guideline states: 'Sentences should be no more than about 20 words. It is better to use a couple of sentences rather than one longer sentence, especially for new information.' Line 33 is in conflict with this guideline.
c. This does not give advice *not to start taking any new medicines while taking X*, without asking their doctor or pharmacist, which is a more likely scenario.
d. This sentence frequently causes confusion, certainly when several medicines are prescribed at the same time. 'Tell your doctor if you are taking any other medicine' indicates that he/she is not aware of the other medicines that a patient might take. If a patient visits different doctors, than this is logical. But for medicines that are always taken in combination under close supervision of a specialist, this is confusing. 'Of course my doctor knows what I'm taking: he/she prescribed it himself/herself.'
e. If the package leaflet must 'enable the user to tell their doctor/pharmacist about all their medicines, than that should be investigated: 'Do users tell their doctor/pharmacist about all their medicines and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
f. 'Please' is nearly always redundant, and dilutes the message.

[Interactions with herbal or alternative therapies should be addressed where necessary.]

g. Test-participants frequently ask about interactions with 'recreational drugs', sport centre vitamins and energy boosting drinks. The template does not really allow to position the use of medicines in a real world context. Taking medicines is separated from all other activities. This is not how patients perceive it. Patients have to integrate their illness and taking medicines into their normal daily lives. Again, this statement is only valid for some types of contexts: not all medicines are the same.

[Interactions with food and drink.]

Line 34: **<Taking> <Using> X with food and drink**

Comments about line 34:

a. People frequently expect instructions on 'how to take a medicine' here. It needs to be clear that only 'interactions' are mentioned here, and that instructions follow in section 3. This subsection should be included only in exceptional circumstances — for example, if the medicine is likely to be dangerous if taken by heavy drinkers.
b. In many situations, it is essential to repeat the interactions again as warnings in section 3. Warnings are most effective when they are placed immediately next to the action or situation that causes the danger. That means that these interactions must be mentioned or repeated in section 3.
c. The Directive mentions interactions with 'alcohol, tobacco, foodstuffs'. The template ignores the interactions with tobacco. The link with alcohol is made in the English language, where 'a drink'

usually means an alcoholic beverage. Unfortunately, this common interpretation is rarely acknowledged in the text that follows this heading.

d. The heading suggests that a medicine X can be taken with food and drink. This interpretation is potentially very dangerous for those medicines that must not be used in combination with any food or drink. The prominence of the heading supports this interpretation.

[Interactions not related to medicinal products should be mentioned here. For example, patients should not consume milk in combination with tetracyclines and no alcohol should be consumed during treatment with benzodiazepines. Where relevant, guidance should always be included to clarify if the medicine must be taken with food, during/before meals, or clearly state if food/meals have no influence, etc.]

e. This is very confusing because it can lead to a repetition of instructions for use. People quite correctly point out that these instructions should not be in a section with a heading 'Before you use/take X'. This user reaction points to a conflict between article 59,1 of the Directive that stipulates the order, and article 59,3 that states that the leaflet must results of consultations with target patient groups.
f. The advice 'where relevant' in the annotated template is not very helpful. It suggests that MAH would like to include irrelevant information. It would be more beneficial to indicate exactly in which situations this guidance should be applied. The reactions of patients during readability tests indicate that this is very rarely relevant.

Line 35: **Pregnancy and breast-feeding**

Comments about line 35:

a. The spelling of the word 'breast-feeding' in the template and 'breastfeeding' in the Directive varies. There is a hyphen in the template which does not appear in the Directive. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. The use of a different spelling for the same word is in conflict with this QRD decision.
b. In UK English, it is correct to write 'breast feeding' (two words), and to hyphenate only when it is used as an adjectival phrase. Writing it as one word is likely to confuse users, who will not recognise it and may have difficulty reading it if their reading skills are less sophisticated.

[Where the information is significantly different, pregnancy and breast-feeding information can be presented under separate headings.]

[Include conclusion summary of the information given in the SPC, in addition to the following optional statement:]

Line 36: <Ask your <doctor> <or> <pharmacist> for advice before taking any medicine.>

[Information on teratogenicity in patient understandable language, should be included in the leaflet when the product is contra-indicated during pregnancy.]

Comments about line 36:

a. This is in conflict with the information provided earlier in the template, and with the statements in the Directive. Contra-indications must be mentioned under 'Do not <use><take> X'. This advice is provided under the wrong heading.
b. The spelling of the word 'contra-indications' differs from 'contraindications' that is used just before line 25. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. The use of a different spelling for the same word is in conflict with this QRD decision.

[Effects on the ability to drive or to use machines.]

Line 37: **Driving and using machines**

Comments about line 37:

a. Patients are frequently confused why this information is provided under the heading 'Before you take X'. It clearly is only applicable after a patient has taken a medicine. No one looks here for the information. Most people look under 'Possible side effects'. The only ones who find it easily are those who spotted it earlier during the interview. The creation of the extra level 1 heading 'While you are taking X' led to improved scores, and improved perception of the leaflet, in diagnostic testing.
b. The action that needs to be enabled is unclear. This section usually contains a warning that the medicine might cause effects that hamper the safety of driving or using machines. Patients interpret that correctly as 'It is unsafe to drive after you have taken this medicine'. However, many patients interpreted this as: 'If you have to drive, do not take this medicine.' This leads to non-compliance: 'I'll have to take it when I come back.'

Line 38: <Do not drive <because...>.>

Comments about line 38:

a. There is no wordspace between 'because' and '…'. This is in conflict with the EMEA guidance on 'consistency'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. The use of a double wordspace is in conflict with this QRD decision.
b. This information is in the wrong place. The statement starts from the assumption that the medicine has been taken, or has been administered. It must be in section 3, because it only occurs after taking the medicine. If it is a warning, it should be presented as such: 'Do not drive after you have taken this medicine' or 'take this medicine only if you do not have to drive for the next xx hours.' Again, this is only applicable to some medicines.
c. If there are any effects of a medicine that might influence the ability to drive or to use machinery, then this must be mentioned in section 4 too. A general statement like: 'This medicine might make you drowsy. Do not drive or operate machinery during your treatment with X' is seen as 'legal cover' if 'drowsiness' is not mentioned in section 4 too.
d. It is not clear why the right indentation of this particular sentence is put as '- 0,05 cm'. Most other sentences do not have a negative right indentation.

Line 39: <Do not use any tools or machines.>

Comments about line 39:

a. It is frequently not clear what is exactly meant by 'tools'. A pair of scissors, a bread knife and a screwdriver are considered 'tools'.
b. It is not clear why the right indentation of this particular sentence is put as – 0,05 cm. Most other sentences do not have a right indentation.

[Excipients warnings.]

Line 40: **Important information about some of the ingredients of X**

Comments about line 40:

a. The phrasing of this heading is questionable. The first word is 'Important'. The word 'Important' is incongruous (and implicitly patronising) here. Are we implying that the rest of the information

is **not** important? This is clearly incorrect. The second word is 'Information'. This strengthens the claim of line 1, but does not help patients much. The statement about 'some of the ingredients' implies that other ingredients are not discussed. The difference between 'ingredients' and 'active substance' is rarely spotted by test-participants.

b. This subheading is the longest of the whole leaflet. It also takes a fairly prominen place at the end of section 2, just before section 3. These factors attract the attention of readers. This extra attention is incorrect: it is likely that for the majority of patients other information is more relevant.
c. It is not clear which user action would be enabled by this statement. Strong evidence from diagnostic testing indicates that this generic subheading is not helpful for users, and does not enable them to find specific information about potentially problematic excipients.
d. The excipients guideline introduces a series of new conflicts with the QRD-template, the Readability guideline and the EMEA-guidelines.
e. Participants in readability tests struggle to find this information under this heading. A more suitable subheading might be: 'X contains lactose' or 'X contains gelatine'.

[If appropriate, details of those excipients knowledge of which is important for the safe and effective use of the medicinal product and included in the guideline on "Excipients in the Label and Package Leaflet of Medicinal Products for Human Use" (The rules governing medicinal products in the European Union, Volume 3B), including relevant warnings for residues from the manufacturing process.]

Comments about line 40 (continued):

f. This instruction in the annotated template is not very clear. It is in conflict with the Draft readability guideline.
g. Here 'the safe and effective use' is explicitely stated as a user action. The package leaflet must 'enable the user to act appropriately'. The knowledge of excipients is mainly relevant for people with specific allergies. The consequences of using a medicines with 'other ingredients' that could influence the safe and effective use are rarely mentioned. It does not state what a patient would experience, nor how a patient would be able to differentiate between an 'allergic reaction' and 'other reactions'.

   The consequence of this is that 'allergies' are mentioned in several different places in the package leaflet. At the beginning of section 2 in line 26, in the obligatory sentence after line 40, and in some cases in section 4 under 'possible side effects'. This does not help patients with allergies.
h. The 'relevant warnings' must be mentioned here. The 'not so relevant ones' must go somewhere else. Please delete the word 'relevant'.

Comments about line 24 to 40

The annotated template states:

For certain medicinal products not all items may be relevant, in this case the corresponding heading should not be included.

1. The graphic presentation of the QRD-template for 'Text to be selected or deleted as appropriate' are the guillemets. It is not clear why these guillemets are not used to indicate the possibility of deleting the sub-headings in this section. The subheadings in line 25, 28, 32, 34, 35, 37, and 40 must start with a '<' and end with a '>' if the convention that is presented on page 1 of the Annotated template is followed.

SECTION 3.

Line 41: **2 HOW TO <TAKE> <USE> X**

Comment about line 41:

a. The Directive states: 'the necessary and usual instructions for proper use' (article 59,1(d).). For medicines given by healthcare professionals, this heading causes a confusion. The instructions for a patient for an infusion or an injection are: 'Just relax'.

[Additional sub-headings within the headings given below may be included if needed to increase readability.]

Comment about line 41 (continued):

b. See comments about line 24, comment b. This is in conflict with the advise in the Readability guideline.

[Instructions for proper use.]
[The following 4 items can be combined as one paragraph.]

[Dosage.]

Line 42: <Always <take> <use> X exactly as your doctor has told you. You should check with your <doctor> <or> <pharmacist> if you are not sure.> <The usual dose is...>

Comments about line 42:

a. This is in conflict with the EMEA guidance on the word 'should'. The 'compilation of QRD decisions on stylistic matters in product information (February 2008, version 11) states: 'However, in order to offer a more precise indication on the mandatory nature of the advice it is advisable that the word 'should' is avoided wherever possible in the English original itself. Recommend change to: 'Check with your <doctor> <or> <pharmacist> if you are not sure.' 'Should' in UK English does not give a clear, unequivocal message. In addition, it is redundant here.
b. There must be a space between 'is' and '…'.
c. The effect of this order is to discourage reading. If the doctor's instructions are paramount, why read the Package leaflet? Additionally, many people in the UK say that a doctor has nothing to say about taking the medicine. That is dealt with by the pharmacy and the pharmacy label.

[Method and/or route(s) of administration.]
[Method of administration: directions for a proper use of the medicinal product; e.g. "Do not swallow", "Do not chew", "Shake well before use".

d. It is not clear what the difference is between 'proper use' (annotated template) and 'appropriate use' (article 63,2) is.

Route(s) of administration according to "Standard Terms" published by the Council of Europe and an additional patient-friendly explanation may be given if necessary.

e. If the package leaflet must 'enable the user to understand the route(s) of administration, than that must be monitored: 'How can we make sure that the route(s) of administration are understood and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
f. The phrase 'an additional patient-friendly explanation' differs from 'in patient friendly language' that is mentioned in the annotated template in lines 22, 27 and 36.
g. How can anyone establish if the additional patient-friendly explanation is 'necessary'?

Article 63,2 states: 'must enable the user to act appropriately'. If the explanation is necessary to 'act appropriately', then it must be included. If the explanation is not necessary, then it can be omitted. Please delete 'if necessary' from the annotated guideline.

h. The spelling of 'patient-friendly' differs here from the texts used in line 22, 27 and 36. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. The use of a inconsistent spelling is in conflict with this QRD decision.

When applicable, there should be descriptions (if useful with illustrations) of opening techniques for childresistant containers and other containers to be opened in an unusual way.

i. If the package leaflet must 'enable the user to understand the route(s) of administration, then the opening techniques must be monitored: 'How do users open containers and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
j. The spelling of the word 'childresistant' is incorrect. It must be two words: 'child resistant'.

Where relevant, guidance should always be included to clarify if the medicine must be taken with food, during/before meals, or clearly state if food/meals have no influence, etc.]

k. This advice contradicts with the advice in the Draft Guideline. The Draft guideline states: 'Avoid repetition of information by cross-referring to information which is under another heading where this is appropriate.' The same information is mentioned in the section that follows line 34.

[Frequency of administration.]
[Specify if necessary the appropriate time(s) at which the medicinal product may or must be administered.]

l. How can anyone establish if specification of the appropriate time is necessary? If the package leaflet must 'enable the user to understand the route(s) of administration, then the administration at the appropriate time must be monitored: 'Do users take their medicines at the appropriate time and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

[Duration of treatment.]
[If appropriate, especially for products available without prescription, precise statements should be included
on:
• the usual duration of the therapy;
• the maximum duration of the therapy;
• the intervals with no treatment;
• the cases in which the duration of treatment should be limited.]

m. The presentation of this bulleted list is in conflict witht the Draft Guidance on Readability.

[Symptoms in case of overdose and actions to be taken.]

Line 43: **If you <take> <use> more X than you should**

Comments about line 43:

a. This is in conflict with the EMEA guidance on the word 'should'. The 'compilation of QRD decisions on stylistic matters in product information states (version 11, Feruary 2008): 'However, in order to offer a more precise indication on the mandatory nature of the advice it is advisable that the word 'should' is avoided wherever possible in the English original itself.'

b. This subheading is not appropriate for medicines which might be taken in deliberate overdose, or for medicines which are dangerous in overdose. Testing a leaflet for an anti-depressant, an important question is: "What should you do if you think someone has taken an overdose of X, and what symptoms should you look for?". The score was low, because respondents did not recognise this heading as referring to overdose. They said that, although they had seen it, they thought it referred only to a situation where someone has accidentally taken an extra tablet. The subheading was changed to '**If you take too much X**'. In the next round of testing, scores improved, because respondents recognised the key term 'too much' (with the two words kept together on a single line).
c. The word 'should' is patronising. It suggests that somebody else has decided for you how much is best for you. In many circumstances, this must be discussed with the doctor.

[Describe how to recognise if someone has taken an overdose and what to do.]

d. There spelling of the word 'recognise' follows the US-conventional style.
e. If the package leaflet must 'enable the user to recognize the symptoms of an overdose, than this must be monitored: 'Do users recognize the symptoms of an overdose and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
f. If the package leaflet must 'enable the user to act in case of an overdose, then this must be monitored. 'Do users act in case of an overdose and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

[Actions to be taken when one or more doses have been missed.]

Line 44: **If you forget to <take> <use> X**

Comments about line 44:

a. If the package leaflet must 'enable the user to act when doses have been missed, then this must be monitored. 'Do users act when a doses has been missed and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

[Make clear to patients what they should do after irregular use of a product; e.g.:]

Line 45: <Do not take a double dose to make up for a forgotten <tablet> <dose> <…>.>

Comments about line 45:

a. This is an incorrect use of the <…> indication. It would be clearer to use the same convention and state <{…}>.
b. If the package leaflet must 'enable the user to act when doses have been missed, then this must be monitored. 'Do users take double doses and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

[Indication of the risk of withdrawal effects.]

Line 46: **If you stop <taking> <using> X**

[Indicate any effects of interrupting or ending the treatment early, if applicable**.** A statement on the potential consequences of stopping the treatment before finishing the course of treatment and the need for a prior discussion with the treating physician or pharmacist should be included as appropriate in patient understandable language. Indicate withdrawal effects when the treatment ends, when necessary.]

Comments about line 46:

a. The use of 'if applicable', 'as appropriate' and 'when necessary' do not really help here. When is this advice applicable, when is it appropriate, and when is is necessary?

b. If the package leaflet must 'enable the user to recognise effects a withdrawal, then this must be monitored. 'Do users recognise withdrawal symptoms and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
c. If the package leaflet must 'enable the user to contact a doctor or pharmacist before stopping, then this must be monitored: 'Do users contact a doctor or pharmacist before stopping and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

[As appropriate, close this section with:]

Line 47: <If you have any further questions on the use of this product, ask your <doctor> <or> <pharmacist>.>

Comments about line 47:

a. This is a repetition of the sentence mentioned at the beginning of the leaflet. The Draft readability guideline specifically mentions that repetition must be avoided.
b. It is not clear why the word 'product' is used here, while in the rest of the leaflet 'medicine' is used. What is the difference? In the actual leaflet, why use the generic 'this product' or 'this medicine' at all? Use the specific name.
c. This sentence conflicts with the information in line 6. There is a slight conflict between this sentence and the final sentence of section 3. Line 6 states: '<If you have any further questions, ask your <doctor> <or> <pharmacist>.>' There is a difference between 'any further questions' and 'on the use of this product'. It might be clearer to delete 'on the use of this product' in line 47.
d. This sentence is in conflict with the statement at the end of section 6. Line 66 states: *'For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:'* In most package leaflets, people are referred to three different sources, of which the MAH is the first source. Further questions, that is, after the questions have been asked to the MAH, should be answered by a doctor or pharmacist. This is probably not what was intended. For users, the doctor or pharmacist should always be the point of contact; they do not need the MAH rep details, which should be for doctors' or pharmacists' use only.
e. For hospital products 'doctor or nurse' might be more appropriate. The use of the word 'pharmacist' has misled people to think that hospital products are meant for home use.

Note about line 41 to 47

The annotated template states:

For certain medicinal products not all items may be relevant, in this case the corresponding heading should not be included.

1. The graphic presentation of the QRD-template for 'Text to be selected or deleted as appropriate' are the guillemets. It is not clear why these guillemets are not used to indicate the possibility of deleting the sub-headings in this section. The subheadings in line 43, 44 and 46 must start with a '<' and end with a '>' if the convention that is presented on page 1 of the Annotated template is followed.

SECTION 4.

Line 48: **4. POSSIBLE SIDE EFFECTS**

[Description of side effects (frequency according to MedDRA).]

Comments about line 48:

a. The frequency descriptors according to MedDRA are not very useful. Both patients and healthcare professionals have very different interpretations of the descriptors used by MedDRA. Research by Peter Knapp (Leeds university) and David Dickinson shows that verbal descriptors are a lot more effective in conveying thiss information to users.
The whole issue of how to list side effects is hugely complex and difficult. A one-size-fits-all solution may be impossible.
Interviewees often tell that they appreciate having the average frequencies listed, because they find lists of side effects very scary, and are reassured by the relatively low incidences. (However, for someone with a serious side effect, the knowledge that 9999 other people haven't got it is no consolation.) Listing only by frequency can also mask the relative severity.
Also, especially when the list of side effects is long, there is no easy way for people to search for one they think they may be experiencing.
If people are to make their own risk/benefit-based decisions about taking this medication, they do need some indication of probabilities.
Recommendations on this need to be based on comparative diagnostic testing, carried out outside the remit of testing individual leaflets for approval purposes.
b. The frequency indicators of the side effects are negative. In stead of saying 99% of the patients does not suffer any side effects, the presentation is reversed. It states: 'these side effects might affect 1 in 100 patients' and not 'these side effects do not affect 99 in 100 patients'.

[Begin this section with:]

Line 49: Like all medicines, X can cause side effects, although not everybody gets them.

Comments about line 49:

a. This is an irritating statement because it is obvious. Yes, it can cause side effects, that's why we're listing them.

[Describe, if necessary, the actions to be taken. If the patient needs to seek help urgently, the use of the term <immediately> is recommended; for less urgent conditions, <as soon as possible> can be used.]

Comments about line 49:

b. Research by Peter Knapp (Leeds University) has shown that these two phrases are interpreted as 'very similar'. People do not interpret this as 'urgently' and 'less urgent', or 'Call emergency or go directly to Accidents and Emergency of your local hospital' or 'at the first opportunity'. There are significant problems for patients understanding side effect data (Berry, Knapp, Raynor. Lancet 2002 pp 853-854), suggesting that the readability guideline ought not to be followed here.
c. The advice 'Describe, if necessary, the actions to be taken.' is in direct conflict with article 63 that states that Package leaflets 'must enable the user to act appropriately'. The words 'if necessary' must be deleted from the annotated template.
d. At the moment, according to the template, patients only need to take tell their doctor if any side effect gets serious, or if they notice any side effect that is not mentioned in the package leaflet'. If there is a side effect that is not considered to be serious by patients, a doctor might not be informed.
e. It is unclear what is expected from patients. The package leaflet does not tell the user what to do with this information. Three options are:
1: Read it while they consider taking the medicine. This is usually before people take it. This is

part of a risk-benefit decision.
2: Read it after having taking the decision to take the medicine. The list of side effects is now seen as 'something to remember if it ever occurs'.
3: Read it when a side effect occurs.

None of these three ways of reading is supported at the moment.
1. The benefits are described in section 1 in a few words. (Research has shown that more information here is very beneficial and appreciated by patients. (Vander Stichele, Gent University)). The risks are described in a substantial list in section 4. Comparing these two requires a lot of mental gymnastics and handling the leaflet. If package leaflets must 'enable the user to make a risk-benefit decision', than this section fails.
2. The list is not put into a format that makes it easy to remember. The sequence has to balance the 'frequency' (how often?) and 'severity' (how serious?).
3. The list of side effects does not make it easy to find a particular side effect when it occurs.

f. The necessity to include all side effects is based on Directive 2001/83 which states that the information must be 'full and comprehensible'. In practice, many test-participants ask questions about this. Some side effects cannot be noticed by patients, such as for example 'an increase in red blood cells', or 'Thrombocytopenia (low blood platelet count)'. Mentioning these frequently confuse patients. It is important to distinguish between effects actually experienced by users (tiredness, dizziness, unexplained bruising, etc.) and effects (which may be the underlying cause of the symptoms) such as anaemia and thrombocytopenia.
g. It is not clear why the right indentation of this particular sentence is put as – 0,05 cm. Most other sentences do not have a right indentation.

Line 50: 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>.

Comments about line 50:

a. This is a repetition of the sentence mentioned at the beginning of the leaflet in line 7. The Draft readability guideline specifically mentions that repetition must be avoided. If the QRD-template overrules the Draft Readability guideline, then that must be stated.
b. 'Please' is nearly always redundant, and dilutes the message.
c. 'If any of the side effects gets serious…' The singular form of the verb is correct in English. 'get' is a word with multiple meanings. 'become' might be more appropriate, although it is longer. 'become' could be less ambiguous for someone whose first language is not English.
d. Users may not be in a position to judge whether a side effect is 'serious'; that is a medical judgement. The words 'severe or troublesome', better describe people's subjective experience of side effects (in UK English, at least).
e. The cover-all statement at the end of Section 4 tells people to 'tell your doctor or pharmacist'. This is interpreted as being a non-urgent action (some interviewees describe the advice as 'casual'). In interviews, people often see this and give it as the action to take for any side effect, which may be very dangerous in practice. For some side effects, this is not the appropriate action, and this statement directly contradicts the warning to get immediate medical attention. Many interviewees have pointed out this contradiction. This is an important safety issue, and should be addressed.
f. This sentence must appear at the end of the section. This location of the instruction is frequently overlooked by test participants. It is particularly hard to find if it appears after a long list of side effects. The instruction what to do if a patient worries about the effects of a medicine must be mentioned before the effects are described.

[Some further notes are given earlier: line 7.]

SECTION 5.

Line 51: **5. HOW TO STORE X**

[For storage conditions statements see Appendix III]

Comments about line 51:

a. It is not clear why this phrase appears in the template. All references to other documents are mentioned in the annotated template. Apart from this one.

Line 52: Keep out of the reach and sight of children.

Comments about line 52:

a. Although it is laudable to protect children at all times and at all costs, there are some circumstances in which this statement is not applicable. Medicines that are used in hospitals only must now carry this warning. It costs time and effort to consciously skip this message when it is not relevant.
b. If the package leaflet must 'enable the user to keep medicines out of the reach and sight of children, then this must be monitored. 'Do people keep medicines out of the reach and sight of children and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

Line 53: Do not use X after the expiry date which is stated on the <label> <carton> <bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.>

Comments about line 53:

a. This is seen by patients as an item that belongs to the list 'Do not use X if …'. It is hard to explain that this appears at the end of the leaflet, while the information is clearly applicable before a medicine could be taken.
b. For most intravenous medicines, this phrase incorrectly suggests that patients must check the expiry date. That is not the case in practice.
c. The full stop after the } is incorrect. It should be }>. In order to end this sentence with a full stop, it would be obligatory to include 'after {abbreviation used for expiry date}.' in every leaflet. If that is the intention, than the guillemets must be deleted.
d. If the package leaflet must 'enable the user to check the expiry date, then this must be monitored. 'Do users check de expiry date and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

Line 54: <Do not use X if you notice {description of the visible signs of deterioration}.>

Comments about line 54:

a. This is seen by patients as an item that belongs to the list 'Do not use X if …'. It is hard to explain that this appears at the end of the leaflet, while the information is clearly applicable before a medicine could be taken.
b. If the package leaflet must 'enable the user to notice visible signs of deterioration, then this must be monitored. 'Do users notice visible signs of deterioration and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.

Line 55: <Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.>

Comments about line 55:

a. A comment made by patients is that they try to give unused medicines back to pharmacists, but that they frequently do not have a disposal system either. This is country-dependent. It should be possible to localise the advice (with some guidance for individual markets).
b. The text now suggests that asking is sufficient. It does not tell you what to do if the pharmacists says 'I don't know'.
c. Asking a pharmacist in itself does not protect the environment.
d. This is in conflict with the EMEA guidance on the word 'should'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: 'However, in order to offer a more precise indication on the mandatory nature of the advice it is advisable that the word 'should' is avoided wherever possible in the English original itself.
e. 'waste water' is usually spelled as two words.
f. It is very hard to find this information under the heading of section 5 'How to store X'. In a few patient interviews, I asked 'How do you dispose of this product' and participants had a real hard time finding these phrases. Most leaflets would fail a readability test if this question is asked.
g. If the package leaflet must 'enable the user to dispose their medicines correctly, then this must be monitored. 'Do users dispose their medicines correctly and do we find that appropriate'? Otherwise, there is a direct conflict with article 63,2.
h. The word 'measure' is inappropriate. Patients do not refer to 'measures' if they have to ask a pharmacist about disposal of medicines.
i. It is an insult to expect that patients do not want to protect the environment.

SECTION 6.

Line 56: **6. FURTHER INFORMATION**

Comment about line 56:

a. For patients, the title 'Further information' is deceptive. They expect more details about the previous sections, and they only get data about the medicine and the manufacturers. It might be worth considering to use a different wording for this heading.

Line 57: **What X contains**

[The active substance(s) (expressed qualitatively and quantitatively) and the other ingredients (expressed qualitatively) should be identified using their names as given in the SPC and in the language of the text, e.g.]

Comment about line 57:

a. It is not clear why there is an empty line after this heading.
b. The final abbreviation e.g. is hard to understand. The subsequent two lines are obligatory text in the package leaflet. The meaning 'for example' is incorrectly used here.

Line 58: - The active substance(s) is (are)…

Comment about line 58:

a. It is not clear why there is an empty line after this heading.

Line 59: - The other ingredient(s) is (are)...

Comments about line 59:

a. It is not clear why the 'ellipsis' in line 58 differs from the 'ellipsis' in line 59. The spacing between the full stops varies.
b. It is not clear what patients have to do with this information: Which user action must be enabled by the provision of this information? Especially if this information is mentioned in line 26 and line 40 already.

Line 60: **What X looks like and contents of the pack**

Comments about line 60:

a. This subheading suggests that the following text contains information that is meant for identification of the product. The Directive clearly positions this at the beginning of the leaflet.
b. The Directive requires: 'for each presentation of the product, the pharmaceutical form and content in weight, volume or units of dosage'. This information is not covered by the subheading.
c. It is not clear why this list is followed by 2 empty lines.
d. It is not clear what patients need to do with this information. If it is to 'identify', than it should be mentioned somewhere with the other information that is used to identify a medicine.

Line 61: **Marketing Authorisation Holder and Manufacturer**

Comments about line 61:

a. It is not clear why there is an empty line in the template after this heading.
b. It is not clear why 'Manufacturer' is spelled with a capital M.

c. The sequence of this item is in conflict with article 59 of the Directive that states that the name and address of the MAH (vi) must be mentioned before the name of and address of the manufacturer (vii).

Line 62: {Name and address}

No comments about line 62:

Line 63: <{tel}>

Comment about line 63:

a. It is not clear why the word 'telephone number' is abbreviated here.
b. In the table - Line 67 - the complete word is used. This is inconsistent.

Line 64: <{fax}>

Comment about line 64:

a. It is not clear why the word 'fax number' is abbreviated here.

Line 65: <{e-mail}>

Comment about line 65:

a. There is a convention that an e-mail address is enclosed between <square brackets>. As example: <waarde@glo.be>. The notation <{e-mail}> is confusing.

Line 66: For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Comment about line 66:

a. There is a direct conflict with the information in line 6 and line 47. Line 6 and line 47 state that patients must contact their doctor or pharmacist with questions about medicines. In this line, patients are advised to contact the local representative.
b. The phrase 'the local representative of the Marketing Authorisation Holder' long and does not mean much to patients.
c. The word 'please' can be deleted.

Line 67:

België/Belgique/Belgien {Nom/Naam/Name} <{Adresse/Adres/Anschrift } B-0000 {Localité/Stad/Stadt}> Tél/Tel: + {N° de téléphone/Telefoonnummer/ Telefonnummer} <{e-mail}>	**Luxembourg/Luxemburg** {Nom} <{Adresse} L-0000 {Localité/Stadt}> Tél/Tel: + {N° de téléphone/Telefonnummer} <{e-mail}>
България {Име} <{Адрес} {Град} {Пощенски код}> Тел.: + {Телефонен номер} <{e-mail}>	**Magyarország** {Név} <{Cím} H-0000 {Város}> Tel.: + {Telefonszám} <{e-mail}>

[Other cells are deleted.]

Comments about line 67:

a. This list is very often resented by test-participants. It is seen as a waste of space and paper. If patients look at these addresses, they frequently ask why they need to know the addresses abroad. The leaflet never contains all languages. Mentioning only those addresses that will respond in the languages of the leaflet would be a real improvement.
b. The inclusion of international telephone codes is hard to rationalise, and should be reviewed. There is no practical situation in which a patient would need to dial abroad. The first point of contact must be a doctor or pharmacist.
c. It is not clear why this list is followed by 2 empty lines.

Line 68: **This leaflet was last approved in** {MM/YYYY}.

Comments about line 68:

a. It is not clear why this phrase is presented in bold type on the QRD-template.
b. It is not clear why the date in this phrase is presented in roman type. This visually distinguishes the date, without a clear reason.
c. Although it is very useful to have a date on the package leaflet, it is unclear what patients need to do with it.
d. It is not clear who approved it. Although the names of the MAH are mentioned, these are clearly not the authority who has approved the leaflet. It would be useful to mention which authority has approved the leaflet. This could reassure patients that the information in the package leaflet has been checked.

Line 69: <This medicine has been given “conditional approval”.
This means that there is more evidence to come about this medicine.
The European Medicines Agency (EMEA) will review new information on the medicine every year and this leaflet will be updated as necessary.>

Comments about line 69:

a. The phrase ‘every year’ is in conflict with ‘review new information’. If the review is every year, than the information cannot be new anymore. Please delete ‘every year’.
b. For some kinds of medicines, this information is vital for patients. For example, patients who use anti-HIV medicines would like to see this information right at the beginning of the leaflet.
c. It is not clear why this information must be presented in three paragraphs. The sentences belong together and two paragraph breaks can be deleted.

Line 70: <This medicine has been authorised under "exceptional circumstances".
This means that <because of the rarity of this disease> <for scientific reasons> <for ethical reasons> it has been impossible to get complete information on this medicine.
The European Medicines Agency (EMEA) will review any new information on the medicine every year and this leaflet will be updated as necessary.>

Comments about line 70:

a. It is not clear why this paragraph is followed by 2 empty lines.
b. There is a double wordspace between 'has' and 'been', between 'on' and 'this', and between 'medicine' and 'every'. The 'compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states: Inconsistencies of style are often found in product information; e.g. punctuation, symbols, spacing, redaction style etc. The use of a double wordspace is in conflict with this QRD decision.
c. The word 'any' in the last line of the 'exceptional circumstances' does not appear in a similar line in the 'conditional approval' statement. This suggests that the EMEA does not review 'all' new information.
d. The phrase 'every year' is in conflict with 'review any new information'. If the review is every year, than the information cannot be new anymore. Please delete 'every year'.
e. It is not clear why this information must be presented in three paragraphs. The sentences belong together and two paragraph breaks can be deleted.

[It is recommended that the following reference to the EMEA Website is included:]

Line 71: <Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.> <There are also links to other websites about rare diseases and treatments.>

Comments about line 71:

a. The spelling of 'Website', 'websites' or 'web site' is not consistent in the template.
b. The website http://www.emea.europa.eu/ is not usable by anyone who does not speak English. There is no navigation in any other language. The links to other websites about rare diseases and treatments are very hard to find if you do not read English.

Line 72: <----------<The following information is intended for medical or healthcare professionals only:>>

Comments about line 72:

a. Can this sentence be shortened to: 'Information for professionals'? This would keep the style of the heading more in line with Line 1: 'package leaflet: information for the user'. Alternatively, Line 1 could be changed to: The following information is intended for patients or people who handle medicines only'.

Note on line 1 – 72.

a. The EMEA 'Compilation of QRD decisions on stylistic matters in product information' (February 2008, version 11) states that 'Excessive use of trade name an unnecessary repetition in SPC and package leaflet/insert' is a problem. The guideline suggests to 'Avoid unnecessary repetition in all product information'. The reference 'X' appears 27 times in the template.
b. The whole leaflet is frequently perceived to be 'negative'. There is a strong emphasis on the risks and not on the benefits. The package leaflet as it is based on the QRD-template does not provide much reassurance for patients.

Appendix 2: Clustering the comments.

The comments can be grouped into the following main categories:

1 - Comments related to the development of Package leaflets
- a. writing,
- b. designing,
- c. testing.

2 - Comments related to the combinations of the Regulations, guidelines and other guidance
- a. Directive,
- b. Guidelines,
- c. EMEA-guidance.

3 - Comments related to instructions for the Marketing Authorization Holder.

In each category, the comments are grouped into clusters. Each cluster is introduced by a brief description, an example, the total number of assertions in the same cluster, and a list of references to the comments in appendix 1.

1 - Problems related to the development of package leaflets.

1a. Writing.

The problems in the template related to the writing of the text can be categorized into 7 groups. The clusters in the category 'writing' contain 85 comments.
These groups are:

1 - Too many words
2 - Incorrect use of words
3 - Inconsistent spelling
4 - Not enough information
5 - Provoking the wrong emotion
6 - Awkward use of English
7 - Inconsistent use of words.

1a1. Writing: Too many words.

Description: There are several words and sentences that could be edited to make the text clearer and more succinct. This can range from a single word to complete sentences.

Example:
Line 9: <Read all of this leaflet carefully because it contains important information for you.

The relevance of this sentence in a patient leaflet can be questioned.

- The instruction 'Read' is superfluous – it is the only thing that people can do with written information.
- 'all' is paternalistic and suggests that patients are unable to make decisions what is relevant.
- 'of this leaflet' can be deleted because the person is looking at the leaflet when this sentence is read. For some medicines, it would be useful to consider the context and refer the patient to the outer packaging too.
- 'carefully' is unclear, because it is impossible to read 'carefully'. If there is a difference between 'careful reading' and 'other forms of reading' than this must be made clear.
- 'because it contains important information' might be assumed to be correct. Otherwise the competent authorities and pharmaceutical industry are putting information in medicine boxes that is not important.
- 'for you' is unnecessary. If a person finds a leaflet in a medicine pack that he/she has just purchased in a pharmacy, it is likely that the included leaflet is for the person who bought it.

[This occurs 30 times: 1c, 1d, (1,1), 6a, 8f, 9b, 10d, 13b, 21a, (1-21, 2), 28c, 31b, 33f, 40b, 40a, 40e, 40h, 42g, 47b, 47c, 49a, 50b, 63a, 64a, 66b, 66c, 69a, 70c, 70d, 72a.]

1a2. Writing: Incorrect use of words.

Description: Words that are misunderstood or that have a different meaning for people.

Example:
Line 56: **6. Further information**

The word 'Further' in the title of this section is deceptive. People expect more details about the first 5 sections here, but that is not what is included in section 6.

[This occurs 20 times: 1a, 1b, 1e, 1f, 5a, 7c, 13d, 18a, 22d, 26c, 26g, 32b, 33a, 34c, 35b, 39a, 48a, 49b, 55h, 56a.]

1a3. Writing: Inconsistent spelling.
Description: The template uses nine words in a spelling that diverts from the convention.

Example:
Line 35: **Pregnancy and breast-feeding**

The spelling of the word 'breast-feeding' in the template and 'breastfeeding' in the Directive varies. There is a hyphen in the template which does not appear in the Directive. The correct spelling in English is 'breast feeding' in two words.

[This occurs 9 times: 22b, 24g, 35a, 36b, 42h, 42j, 43d, 55e, 71a.]

1a4. Writing: Not enough information.
There are several points that could help people if a bit more information is given.

Example:
Line 3: **{Active substance(s)}**

The name of an active substance is for patients hard to remember or recognize. In the template, this information is presented without a context. It would be easier for patients if it states: 'Active substance: {active substance(s)}'.

[This occurs 8 times: 3a, 4g, (1-21, 1), 26d, 26i, 27c, 27f, 60b.]

1a5. Writing: provoking the wrong emotion
Description: Some words and phrases are insulting patients, patronize patients and do not reassure patients.

Example:
Line 4: <Read all of this leaflet carefully before you start <taking> <using> this medicine.

In this sentence, 'carefully' is found to be patronizing. It assumes that patients will be reading it in a 'careless' way. There is no evidence to suggest that. 'all of this' is patronizing too. It assumes that patients are not capable of finding the most relevant information themselves.

[This occurs 8 times: 4a, 4b, 7a, 9a, 10b, 10c, 55i, 1-72b.]

1a6. Writing: Awkward use of English
Description: Some of the phrases and sentences in the template do not follow the current conventions on the use of English.

Example:
Line 8: - 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>.>

The plural of 'side effects' conflicts with the singular form of 'gets'. In every interview, every native English speakers stumbles here. After re-reading it is either confirmed to be correct English – 'any' is singular – or a remark is made that it should be 'get' and not 'gets'.

[This occurs 5 times: 6e, 8c, 13c, 31a, 50c.]

1a7. Writing: Inconsistent use of words.
Description: Some descriptions in the Annotated template differ from the texts in Directive 2004/27/EC.

Example:
[The pharmacotherapeutic group or type of activity should be stated here using patient understandable language.]

There is a difference between Directive article 59, 1(a), (i) which states 'in terms easily comprehensible for the patient' and the text that appears in the annotated template: 'using patient understandable language'. If there is no difference, please use the same words.

[This occurs 5 times: 22a, 24e, 42d, 42f, 63b.]

1b. Design: visual presentation

The problems in the template related to the testing of the text can be grouped into the following categories. The groups in the category 'design' contain 48 comments.
These groups are:

1 - inconsistent use of punctuation
2 - inconsistent use of line breaks and indentations
3 - inconsistent use of bold type
4 - inconsistent use of linespace
5 - inconsistent use of wordspaces
6 - confusing use of punctuation
7 - inconsistent use of bulleted lists
8 - inconsistent use of capitals
9 - inconsistent use of centered type

The consequence of these 9 groups is that Marketing authorization holders must put an extraordinary amount of time into the design of the leaflets. Each applicant has the choice between 'leaving the mistakes as they are', or 'trying to remedy the errors'.

1b1. Design: inconsistent use of punctuation.

Description: Punctuation marks are not consisitently applied in the template.

Example:
Line 26: - <if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of X.>

The left guillemet follows the hyphen ('- <'). Now every leaflet must include the hyphen. This is incorrect. The sequence of the punctuation must be: '< -'.

[This occurs 11 times: 2a, 13a, 15b, 26b, 27b, 29a, 30a, 31d, (24-40.1), 45a, (41-47.1).]

1b2. Design: inconsistent use of line breaks and indentations

Description: Line breaks and indentations are not consisitently applied the template.

Example:
Line 38: <Do not drive <because...>.>

It is not clear why the right indentation of this particular sentence is put as '- 0,05 cm'. Most other sentences do not have a negative right indentation.

[This occurs 9 times: 20a, (16-21, 1), 38d, 39b, 49g, 53c, 59a, 69c, 70e.]

1b3. Design: inconsistent use of bold type

Description: The use of bold type is inconsistent or not clear.

Example:
Line 4: **<Read all of this leaflet carefully before you start <taking> <using> this medicine.**

It is not clear why this sentence is presented in bold type. It is now presented as if it is a heading, but it does not fulfill the same purpose.

[This occurs 6 times: 1g, 2c, 4f, 15a, 68a, 68b.]

1b4. Design: inconsistent use of linespaces
Description: The use of linespaces is inconsistent or not clear.

Example:
Line 60: **What X looks like and contents of the pack**

It is not clear why this heading is followed by 2 empty lines.

[This occurs 6 times: 57a, 58a, 60c, 61a, 67c, 70a.]

1b5. Design: inconsistent use of wordspaces.
Description: The template contains both double spaces, as well as missing spaces.

Example:
Line 42: <The usual dose is...>

There must be a space between 'is' and '…'.

[This occurs 6 times: 8b, 27a, 31c, 38a, 42b, 70b.]

1b6. Design: confusing use of punctuation
Description: The template uses punctuation in a confusing way.

Example:
Line 2 and 3: **{(Invented) name strength pharmaceutical form}**
{Active substance(s)}

The function of the '}' at the end of the first line, and the '{' at the beginning of the second line is unclear. These can be deleted.

[This occurs 4 times: 2b, 3b, 5b, 65a.]

1b7. Design: inconsistent use of Bulleted lists
Description: The template presents information in structures that look like bulleted lists. However, these lists do not follow the formats required by the Readability guideline.

Example:
Line 28-31: Take special care with X
- <if you ...>
- <when ...>
- <Before treatment with X,…>

It is not clear if this list is intended as a 'list of bullet points' as it is described in the Readability Guideline. There is a difference between hyphens and bullets, the capitalization of 'Before' and the lack of a colon seems to indicate that this is not a 'list of bullet points'.

[This occurs 3 times: (4-8, 2), 15c, 25a (28-31, 1).]

1b8. Design: inconsistent use of capitals

Description: The use of some capital letters in the template is questionable.

Example:
Line 61: **Marketing Authorisation Holder and Manufacturer**

It is not clear why 'Manufacturer' must be spelled with a capital M.

[This occurs twice: 31e, 61b.]

1b9. Design: inconsistent use of centered type.
Description: The use of centered type in the template is questionable.

Example:
Line 1-3: **PACKAGE LEAFLET: INFORMATION FOR THE USER**

{(Invented) name strength pharmaceutical form}
{Active substance(s)}

It is not clear why these three lines must be centered.

[This occurs once: (1-3, 2).]

1c. Testing

The problems in the template related to the testing of the text can be grouped into the following categories. The groups in the category 'Testing' contain 76 comments.

These groups are based on the comments made by participants of readability tests in the last few years. Participants pointed out that the information in the template:

1. Questionable location.
2. Instruction cannot be followed.
3. Instruction not applicable in context.
4. Information does not match the expectations.
5. Instruction is unclear.
6. Instructions are conflicting.
7. Effect of the action is not beneficial.
8. Instructions are mentioned in different locations.
9. Instructions are incomplete.
10. Reactions of readers are in conflict with the Directive.
11. There might be better alternatives available.

The consequence of these comments is a suboptimal performance of the package leaflet. Test participants get irritated and it increases the anxiety.

This is frequently depending on the context, type of medicine, type of administration, local variations and format of the leaflet.

1c1. Testing: Questionable location of the information.

Description: Some of the information in the template is presented in a location where test-participants do not expect it.

Example:
Line 54: <Do not use X if you notice {description of the visible signs of deterioration}.>

This is seen by patients as an item that belongs to the list 'Do not use X if …'. It is hard to explain that this appears at the end of the leaflet, while the information is clearly applicable before a medicine could be taken.

[This occurs 14 times: 6c, 8a, 26f, 34b, 36a, 37a, 38b, 38c, 50f, 53a, 54a, 55f, 60d, 69b.]

1c2. Testing: Instruction cannot be followed.

Description: patient cannot know or cannot execute an instruction.

Example:
Line 50: 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>.

Users may not be in a position to judge whether a side effect is 'serious'; that is a medical judgement. The words 'severe or troublesome', better describe people's subjective experience of side effects (in UK English, at least).

[This occurs 14 times: 4d, 5e, 8d, (4-8, 1), 17b, 25d, 26e, 27e, 28d, 41a, 42c, 49d, 50d, 53b.]

1c3. Testing: Instruction not applicable in context.

The instruction is not related to practical user-actions.

Example:
Line 4: <Read all of this leaflet carefully because it contains important information for you.

This instruction suggest that people must read the disposal instructions and the list of MAH-representatives before taking the first dose? In practice, it is unlikely that patients read a leaflet in sequential order from the first line to the last line.

[This occurs 11 times: 4c, 5f, 17a, 17c, 20b, 32a, 32c, 33d, 47e, 52a, 55a.]

1c4. Testing: Information in the template does not match the expectations of readers.

Example:
Line 16: **1. What X is and what it is used for**

This title frequently confuses people. For patients, X is a medicine. The question 'What X is' is not the most important question for most patients. 'What it is used for' is more important.

[This occurs 9 times: 16a, 24a, 25b, 26a, 34a, 34d, 43b, 48b, 68d.]

1c5. Testing: Instruction is unclear.
The instruction is unclear: it does not exactly tell what to do.

Example:
Line 10: However, you still need to <take> <use> X carefully to get the best results from it.

How can you take a medicine carefully? How can a patient check if a medicine is taken carefully? If a patient takes it without taking care, will the results be worse?

[This occurs 7 times: 10a, 28a, 40c, 43c, 67a, 67b, 68c.]

1c6. Testing: Instructions are conflicting
Description: Instructions are in conflict with eachother.

Example:
Line 6: If you have any further questions, ask your <doctor> <or> <pharmacist>.

This sentence is in conflict with the statement at the end of section 6. Line 66 states: *'For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:'* People are referred to three different sources, of which the MAH is the first source. Further questions, that is, after the questions have been asked to the MAH, should be answered by a doctor or pharmacist. This might not be the most approapriate way to deal with questions from patients.

[This occurs 4 times: 6b, 47d, 50e, 66a.]

1c7. Testing: Effect of the action is not beneficial
Description: The effect of an action is unlikely to be beneficial (help environment, more information available, inappropriate behaviour=non-compliance) 'even if you do it, it still doesn't help.'

Example:
Line 55: Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.>

Asking a pharmacist in itself does not protect the environment.

[This occurs 4 times: 37b, 55b, 55c, 71b.]

1c8. Testing: Instructions are mentioned in different locations.
Description: Information is presented in different locations in the leaflet in such a way that this does not suppport the action: it is unclear which action is exactly expected.This happens with the list of side effects, the excipients and the description of the pack.

Example:
Line 60: What X looks like and contents of the pack

This subheading suggests that the following text contains information that is meant for identification of the product. The Directive clearly positions this user action at the beginning of the leaflet.

[This occurs 4 times: 40g, 49e, 59b, 60a.]

1c9. Testing: Instructions are incomplete.

Example:
Line 33: <Please tell your <doctor> <or> <pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.>

This does not give advice *not to start taking any new medicines while taking X*, without asking their doctor or pharmacist, which is a more likely scenario.

[This occurs 4 times: (1-21, 3), (16-21, 2), 33c, 33g.]

1c10. Testing: Reactions of readers are in conflict with the Directive (Sequence, completeness, easy to use).

Example:
Line 34: **<Taking> <Using> X with food and drink**

This is very confusing because it can lead to a repetition of instructions for use. People quite correctly point out that these instructions should not be in a section with a heading 'Before you use/take X'. This user reaction points to a conflict between article 59,1 of the Directive that stipulates the order, and article 59,3 that states that the leaflet must results of consultations with target patient groups.

[This occurs 3 times: 32d, 34e, 49f.]

1c11. Testing: There might be better alternatives available.

Example:
Line 1-21: From the first line to the end of the contents list.

The comments of Readability test participants seem to imply that it would be worth investigating if

this space could not be better used to – for some products only – mention the 'most important points'. These could be the main points that a user must know about a specific medicine. The current points are applicable to all medicines. It might be more beneficial to make them specifically applicable to a single product.

[This occurs twice: (1-21,4), 25c.]

2 - Conflicts with legislation and guidance.

These comments are related to a comparison of advice and legislation.

2a1 Conflicts: Directive Article 63,2 and article 59,1.
There is a fundamental conflict between article 59 and article 63,2 of the Directive. Article 59,1 states that specific information elements must be mentioned in a specific order in the package leaflet. Article 63,2 states that information 'must enable the user to act appropriately'. In several situations, the 'user is not enabled to act appropriately' by the information elements that must be used in the package leaflet. The template followed article 59 to a large extend, and ignores article 63,2.
The template is in conflict with article 63,2 in 28 cases.

Example: Line 26: - <if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of X.>

If the package leaflet must 'enable the user to detect an allergic reaction, then this must be monitored'. The question that must be asked according to article 63,2 is: 'How can we avoid that people use medicines if they are allergic to the active substance or other ingredients, and do we find that appropriate'? If this question is not asked, investigated and answered, it is not possible to conform to article 63,2.

[This occurs 28 times: (1-3, 1), 4e, 5c, 5d, 5g, 6d, 7b, 8e, 9c, 10e, 12a, 13e, 26h, 27d, 33e, 42e, 42i, 42l, 43e, 43f, 44a, 45b, 46b, 46c, 52b, 53d, 54b, 55g.]

2a2 Conflicts: Directive Sequence
The template conflicts with article 59,1 of Directive 2004/27/EC on seven occasions. This article states that the information in the package leaflet must be given in a specific order. The template follows this order in most details, but there are some deviations.

Example:
Line 31: **<Taking> <Using> X with food and drink**
[Information in patient understandable language, special warnings and appropriate precautions for use should be provided here.]

This advice is in conflict with Directive 2004/27/EC. At this point, the information that is required in section 59,2(c), (iv) is placed before the information that is required in section 59, 2(c), (iii). This is in conflict with article 59,1 that states that the information must be given in a specific order. The information about 'special warnings' must appear **after** the 'forms of interaction'.

[This occurs 7 times: 16b, 22c, 24f, 28b, 31f, 36a, 61c.]

2a3 Conflicts: Directive Ignored (not mentioned).
Section 1 could contain information about the situation that needs to be treated, a description how a medicine changes this situation, and a description of the desired outcomes. Additional information in this section does benefit patients (Vander Stichele, University Gent) and would be perfectly in line with article 62: *'The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of the product characteristics which is useful for the patient, to the exclusion of any element of a promotional nature.'* Unfortunately, this article 62 is ignored in the QRD-template.

[This occurs once: 22e.]

2b Conflicts with the Readability Guideline

Example:
Line 24: **2. BEFORE YOU <TAKE> <USE> X**

The annotated template suggest that it is possible to include 'additional sub-headings within the headings given below.' The template has two levels of headings at the moment. Additional sub-headings would create a third level of heading. This is in direct conflict with the advice in the Draft Readability Guideline. This guideline states: *'The use of multiple levels of headings should be considered carefully, as more than two levels may make it difficult for patients to find their way around the leaflet.'*

[This occurs 14 times: 1g, 1i, 3c, 24b, 31g, 33b, 40d, 40f, 41b, 42k, 42m, 47a, 49c, 50a.]

2c. Conflicts: EMEA stylistic guidelines.
The 'compilation of QRD decisions on stylistic matters in product information' states: 'However, in order to offer a more precise indication on the mandatory nature of the advice it is advisable that the word 'should' is avoided wherever possible in the English original itself. The word 'should' appears three times in the template.

Example:
Line 42: <Always <take> <use> X exactly as your doctor has told you. You should check with your <doctor> <or> <pharmacist> if you are not sure.> <The usual dose is...>

The 'compilation of QRD decisions on stylistic matters in product information states: 'However, in order to offer a more precise indication on the mandatory nature of the advice it is advisable that the word 'should' is avoided wherever possible in the English original itself.

[This occurs 4 times: 42a, 43a, 55d, 1-72a.]

3 - Unclear instructions for the Marketing authorization holder.

3a. Instructions are not specific enough or are unclear.

Example:
Line 23: <This medicine is for diagnostic use only.>

It is not clear why 'medicines for diagnostic use' are separated here. For patients, this statement does not help very much. If it is vital to make a special statement about this group of medicines, than there must be a motivation in the Annotated template.

[This occurs 7 times: 23a, 24c, 24d, 31h, 34f, 46a, 57b.]

3b. Instructions are provided in the wrong location.

Example:
[For storage conditions statements see Appendix III]

It is not clear why this phrase appears in the template. All references to other documents are mentioned in the annotated template. Apart from this one.

[This occurs once: 51a.]