

**Analysis and Evaluation of the QRD Human Product Information Template
used in Package Leaflets**

Dissertation proposal

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under the supervision of Professor Dr. rer. nat. habil. Harald G. Schweim
at Department of Regulatory Affairs,
Rheinischen Friedrich-Wilhelms-Universität Bonn

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1. Summary

All medicinal products must be accompanied by a package leaflet as defined in the European medicine act (Directive 2001/83/EC) [1]. Article 59 (3) of this directive states that ‘the package leaflet shall reflect the results of consultation with target patient groups to ensure that it is legible, clear and easy to use’. In an attempt to provide unity within the European Community, the Working Group on the Quality Review of Documents (QRD) was established in June 1996 [2]. The QRD template produced by this working group reflects the following requirements of Directive 2001/83/EC for package leaflets: the contents and their order. Furthermore, this template is a text frame and provides headings for paragraphs and sub-paragraphs and the wording of specific information [5]. The QRD-Working Group will publish a revised version of the QRD template in May 2011 for centralised approved medicines, namely version 8 [4]. The planned dissertation is going to investigate this newly published QRD template version with respect to its usability for patients and will compare this edition to its’ predecessor and an alternative version. Therefore, package leaflets for a commonly used medicine will be developed according to template version 7.3.1 [5], the newer version 8 [4] and the alternative. Subsequently, a readability test will be used in a study carried out in the United Kingdom and Germany. This will enable comparison in two languages for different versions of the template. The results of this study could be considered in future versions of the QRD template.

1. Legal and Regulatory background

1.1 European Regulations according to the Medicine acts

Following the thalidomide tragedy in the 1960s, it was decided that rational changes were needed in drug law to ensure the safety of the patient, and since 1999, a patient information leaflet (PIL) has been provided with all medicines distributed within the European Union. These provide information to enable patients to take their medication properly and also be aware of when to seek further medical advice. The package leaflet is therefore a vital source of information, in addition to that provided by healthcare professionals, for the patient about a particular medicine, whether prescribed or bought over the counter.

The European Directive 65/65/EEC [6] provided the first laws for the production and distribution of medicinal products in order to safeguard patient health, although here the inclusion of a package leaflet was not mandatory. Directive 65/65/EEC was amended in 1975 by Directive 75/319/EEC [7]. Minimal criteria were defined here for the contents of the package leaflet although its presence in the packaged product was not compulsory and was to be decided by the relevant member state. The implementation of Directive 89/341/EEC in 1989 first made the inclusion of a package leaflet compulsory [8]. In Article 6, the final subparagraph was replaced by the following: 'The inclusion of a package leaflet in the packaging of medicinal products shall be obligatory unless all the information required by this Article is directly conveyed on the container itself and the outer packaging'. With the introduction of the European Directive 92/27/EC [9], further particulars to be described in the package leaflet and on the outer and immediate packaging were defined. This Directive was later revised by Directive 2001/83/EC [1] which dealt mainly with disparities between certain national rulings and attempted to assemble them in a single text in order to safeguard public health within the member states of the European Community. Subsequently Directive 2004/27/EC [10] amended Directive 2001/83/EC. Article 59 in these directives defines the contents of the package leaflet. This resulted in the following requirement provided by Article 59 (3): 'the package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use'.

2.2 Country specific regulations in Germany and the United Kingdom

2.2.1. Germany

Due to regulations to create a united Europe, the Federal Ministry of Health was founded in Germany in 1961. The German Drug Law (AMG) of 1976, which came into force on 1 January 1978, made the inclusion of a package leaflet compulsory [11]. In a second amendment of this ruling in 1986, the role of the summary of product characteristics for medical professionals was more clearly defined [12]. In Germany, user-testing became a requirement when the 14th amendment to German drug law (§22) came into force, but only for medicines receiving marketing authorization after September 2005 [11]. In Germany the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)) is responsible for approving the patient information leaflets supplied with a medicine. German Drug Law provides clear guidelines on the required order of sections which must be contained within the package leaflet.

2.2.2. United Kingdom

In the United Kingdom, some form of medicine regulation existed since the time of King Henry VIII, but it was first in 1971 that a comprehensive regulatory system was introduced [13]. The Medicines act from 1968 was brought in force to govern the manufacture and supply of medicine [14] and subsequently the Misuse of Drugs Act was implemented in 1971 to control the use and supply of narcotic drugs and psychotropic substances [15]. Two executive agencies were responsible for overseeing and enforcing the legislation: the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA), which in April 2003 merged to become the Medicines and Healthcare Products Regulatory Agency (MHRA). The Medicines act controls manufacture, sale, supply and importation of medicinal products into the UK. Here, the package leaflet is mentioned as being obligatory before the product can be supplied to the patient although regulations regarding the content are not mentioned. In the United Kingdom, it was a legal requirement that all marketing authorization holders submit applications to update marketing authorizations with an approved patient information leaflet to comply with article 59 (1) of the council Directive 2001/83/EC by 1 July 2008 [16]. The MHRA is responsible for approving these patient information leaflets.

2.3 Status of the package leaflet

The package leaflet must meet the needs of a wide range of users and therefore it is in the interest of pharmaceutical companies to produce readable and patient friendly information. Better communication aided by written information has been found to generally increase patient satisfaction [17, 18], although it has been reported that the patient information leaflet is only read by about 50 % of patients [18]. It is well known that patients forget or misunderstand much of what is said during consultation with a doctor and it has been found that on average patients had forgotten half of what the doctor told them within 5 minutes of leaving the surgery [17]. Here, the package leaflet is a vital source of information for when the patient returns home. For medicines bought over the counter for common ailments, the patient can have had no contact with a health professional making the role of an understandable package leaflet of critical importance. This is especially the case in the United Kingdom where many medicines can be bought in supermarkets and via the internet.

Previously, lack of information was described as a major factor for why patients do not take their medicine as prescribed [19]. This does not reflect the current situation and package leaflets are getting longer and longer due to the patients' rights to information in order to make an informed decision regarding their medication, various country specific and European regulations [9, 20] which regulate the contents of the package leaflet, and the fact that pharmaceutical companies can be made liable to pay compensation if a person is substantially damaged due to missing information which does not reflect current medical knowledge (Section 84, AMG [20]). One study quotes that 42 % of consumers think that the package leaflet is too long [21]. An analysis of 68 package leaflets in Germany showed that one in five actually contained more than 2000 words [22].

Surprising however, is that this increased content does not reflect the fact that many leaflets still do not contain the information required by the patient for safe use. A survey of 271 German package inserts showed that only 29.5 % listed the maximum daily dose for all users and 54.6 % provided actions for all possible side effects [25] clearly

illustrating that increased length has not improved safety information. Patient motivation to completely read a package leaflet is clearly improved by a shorter text and a maximum content of 1500 words has been suggested [24]. Extensive information has not been shown in general to reduce the comprehension of a particular leaflet but moreover reduces the chance of finding particular information [25]. The ease of locating certain key messages was also shown to be decreased in relation to an increase in the percent of difficult words per total number of words.

Many sections of the package leaflet are considered to be less important than others by the reader, for example, the name and address of the pharmaceutical company and manufacturer [22, 26]. In contrast, the indication, dosage instructions and side effects were classed as 'very important'. A study in which patients were asked to classify the importance of the sections of the package leaflet in order of precedence showed that the indication should start the leaflet followed by dose instructions, composition, warnings for use, contraindications, interactions and side effects [26]. This does not completely match the legally defined sequence of sections as using a logical order requires that contraindications and special warnings must be provided before patients use the dosage instructions. However, the current order of information does better reflect patients' requirements than the version before Directive 2004/27/EC came into force [27].

Specialists have reported that patients frequently have less confidence in their medicine after reading the package leaflet [27]. The consequence of 'less confidence' in a particular medicine due to the complex and detailed information contained in a package leaflet can lead to the problem of non-compliance which has been suggested to be a 'side-effect of drug information leaflets' [28]. This can have major economic implications on one hand via product loss [29]. A study carried out in Germany in 1988 and repeated in 1998 revealed that although prescription charges had increased during the 10 year period that the amount of unused drugs brought back to the pharmacies had actually increased. On the other hand, non compliance can also indirectly have monetary effects through the complication of disease management [28]. One example, in the case of patients with hypertension, demonstrates that medical non-adherence is a significant risk factor which leads to poor blood pressure control, thereby contributing to the development of further vascular disorders such as heart failure, coronary heart disease, renal insufficiency and stroke [30]. It has been reported that up to one third to half of patients do not comply to a prescribed treatment regimen and that this non-adherence rate is relatively high across disease states, treatment regimens, an age groups [30]. One study involving people living in the United States of America showed that approximately 25,000 deaths a year can be attributed here to non-adherence [31]. Non-adherence is multi-faceted in the home-setting and often involves using more or less than the prescribed dose, completely not taking certain medicines, taking an extra dose, using an unauthorized medication or taking medication at the wrong time [31]. Although a patient's ability to abide by a certain prescribed treatment regime may be compromised if they cannot understand basic information about the prescribed medicine, other factors such as the perceived severity of the illness and social circumstances may also have an effect.

The package leaflet must be understandable to a wide spectrum of ages and for all levels of education but they are not comprehensible for over a third of the people for whom they were intended [17]. This is a problem which has previously been identified that the majority of package leaflets, regardless of their topic, require relatively high reading skills that may not exist in a large proportion of their target populations [32].

Many of the terms included in a package leaflet are also not clear enough for a patient to understand the meaning such as 'high doses' or 'long term use' [22]. Not all sections of the package leaflet are of equal comprehensibility for the user. In a Swedish study of 30 randomly selected leaflets, it has been found that although patients could recognize and comprehend various information items in the information leaflet, certain sections, namely 'risks of interactions' and 'contraindications' were poorly understood [33]. This was suggested to be due to the complexity of the information contained in these sections.

The legal regulations regarding the contents of the package leaflet from the point of view of the pharmaceutical companies, and the difficulties of the patient in comprehending to some extent the presented information provide a seemingly difficult problem to solve. The European Commission in an attempt to deal with this predicament developed the Readability Guideline.

2.4 **Readability Guideline**

Article 65 of Directive 2001/83/EC [1] refers to guidelines regarding the legibility of particulars on the labelling and package leaflet. In 1998 the European Commission presented the first Guideline on the Readability of the labelling and package leaflet of medicinal products for human use [34] which was updated in January 2009 [35]. The purpose of the Guideline is to lay down general principles to help pharmaceutical companies make the labelling and information in the package leaflet legible and comprehensible for the patient. Guidance is given on presentation of the labelling and package leaflet, and a method of how a test of a package leaflet can be undertaken. An active writing style rather than passive is suggested to be used and long sentences should be avoided.

In comparison to its predecessor, the Readability Guideline published in 2009 contains substantial information regarding font type and sizing. Whereas in 1998, the font size minimum was 8 pt., this has now been increased to 9 pt. as particularly small font size is often criticized by users as being a reason for poor readability [26]. Although the Readability Guideline states that the minimum font size used should be 9 pt., one survey showed that patients would prefer 10 or even 11 pt. [36].

2.5 **Carrying out a readability test**

In an attempt to improve the situation for the patient regarding the comprehensibility of the package leaflet, Art 59 (3) was included in Directive 2001/83/EC [1]: 'The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use'. The purpose of this article is to ensure that potential patients can locate and understand the key messages contained in a package leaflet. User testing of a package leaflet is one way to demonstrate that this article has been complied with, and data submitted in accordance with this article is assessed to determine whether specific information can be found and understood. The Readability Guideline [35] did not directly refer to a particular method which should be used to test a package leaflet, but does define what requirements are needed for a leaflet to pass the test i.e. the 90 % / 90 % rule.

There are two main methods for user testing: the Australian method, which is most frequently used, or the written readability test which is mentioned in the CMDh position paper also known as the self-completion method [37]. Both are performance- rather than content based i.e. they reflect how the package leaflet performs when participants search for particular information rather than whether the information is actually understood. Other methods are not excluded providing they are suitably validated and appropriate for the purpose.

Both Australian and written readability test methods initially involve the same steps i.e. optimising the leaflet for content and design elements, identifying the key safety messages and subsequent preparation of a questionnaire containing open questions based on the key messages, and some general questions on perception of the document. The Australian method then carries out face-to-face interviews with participants in groups of ten preceded by a pilot test of around 3 participants, whereas in the written readability test, participants in groups of 10 or more complete the questionnaire under observation. Both methods then collate the responses, make revisions if necessary to the package leaflet and carryout a minimum of one further round of testing with 10 participants.

Both methods are similar in the acceptance criteria. The work of the Australians Sless and Wiseman [38] uses the 90 % of 90 % criteria (overall 81 % but in practice 80 %). This method of testing is also supported in the UK by the MHRA [42]: 'A satisfactory test outcome for this method is when 90% of literate adults are able to find the information requested within the PIL, of whom 90% can show that they understand it' per tested information.

The written readability test method aims to remove any negative external influences which may occur during the face-to-face interview in the Australian method [37]. The verbal interview technique would also exclude people with hearing problems. A written readability test method maybe a more realistic monitor of the real-life situation when the patient returns home with a new package leaflet which they have to comprehend alone. Writing skills are however essential for this method of testing and may therefore lead to exclusion of certain subjects which is not within the meaning of article 59 (3). Both test methods require that the participants read the leaflet independently.

3. The QRD templates

The purpose of the QRD template is to ensure that all the information required by Directive 2001/83/EC [1] is included in the text versions of all packaging components in the order specified to provide uniform package leaflets. The annotated QRD template also cross references the use of the Readability Guideline. The Working Group on the Quality Review of Documents (QRD) was established in June 1996 [2]. The QRD template is available as an annotated and non-annotated version on the EMA web site [40]. Headings and standard statements are given in the template which should be used whenever they are applicable. Deviation is possible to accommodate the needs of a specific product but these are considered by the authorities on a case-by-case basis.

Updated QRD template

A newer version of the template is planned to be published in May 2011 and the draft shows a number of changes in comparison to its predecessor. The title of the document now reads: Package Leaflet: Information for the <patient><user> therefore now taking into consideration that the patient himself may not read the package leaflet but rather a carer, nurse or doctor. The term 'this medicine' is currently preferred to continual use of the product name.

The wording contained in the information box at the start of the package leaflet differentiates between over the counter medicines and those only available on prescription. For both types of package leaflet, the patient is told to contact a health professional if they get any side effects, and not only if any of the side effects get serious, as was previously. The contents list of the leaflet has changed in that the title of section 2 now reads 'What you need to know before you <take><use> X' and that of section 6 'Contents of the pack and other information'.

Within the actual package leaflet a number of modifications have occurred which are briefly described below. In Section 1: 'What X is and what it is used for', the benefits of using the medicine may be described. A subheading is suggested of 'How does X work'. An additional text element is now included at the end of the section that the patient must talk to a doctor if they do not feel better or maybe even worse after a certain number of days. In Section 2: "What you need to know before you <take><use> X" the first sentence regarding contraindications now reads "Do not <take><use> X if you are allergic to {active substance(s)} or any of the other ingredients of this medicine (listed in section 6)". The use of the cross-reference to section 6 assists the patient in finding the list of excipients contained in the medicine. The word 'hypersensitive' is no longer used. Following the absolute contraindications, a new heading is included: 'Warnings and Precautions'. A subheading for children and/ or teenagers can be incorporated with potential children/teenager specific warnings. Under the subheading: 'Other medicines and X' the wording has been changed to accommodate the fact that the patient may take other medicines in the future and not just at the present or in the past. The next sub-heading is "X with <food><and><, ><drink><and><alcohol>". Here the inclusion of "alcohol" is new in version 8.

Under the sub-heading 'Pregnancy and breast-feeding', fertility is now recommended to be described if information can be provided. Section 3: 'How to <take><use> X' begins differently for medicines available only on prescription and those sold over the counter. A patient who is prescribed a medicine is told to consult a doctor or pharmacist if they are not sure how to take the medicine while for over the counter medicines the patient is additionally told to take the medicine exactly as described in this leaflet. New in this section is a description of the purpose of the score line. Section 4: 'Possible side effects' should be divided into two parts, a summary of the safety profile as per section 4.8 of the SmPC where the most serious side-effects are listed prominently first with less serious side-effects coming later.

The provided examples of the QRD template changes illustrate major text differences and extension in the volume of text compared to the previous version. The intended dissertation plans to investigate the usability of the updated QRD template.

4. Dissertation work schedule

4.1. Timetable

The following time frame is intended to perform the QRD template study:

- May to July 2011: Analysis of the QRD templates from initial versions to that which is used today.
- August to December 2011: Development of test package leaflets for a commonly used active ingredient
- January 2012: Development of questionnaires for the readability test
- February and March 2012: Pilot test with a small number of participants and the developed materials
- April 2012 to September 2013: Recruiting and questioning participants
- Throughout and following recruiting - up to November 2013: Data input into a file and analysis of obtained results
- 2014: Completion of project

4.2. Analysis of QRD templates

One of the main goals of this dissertation is to identify whether the new QRD template version 8 provides advantages in readability and understanding for the patient in comparison to the previous version. A thorough analysis of past versions of the template will therefore be carried out to begin the project. The new template seems to provide a better structure with clear headings / sub-headings which could lead to better patient understanding. Clearer instructions are additionally included for use in children. Some of the headings in the older versions of the template such as 'take special care with X' were found to be confusing for the patient as the meaning of 'special care' is hard to define [39]. Previous versions of the template were clearly designed to be read by the patient only. The new template has changed this by including the possibility of using the terms 'doctor', 'pharmacist' and 'nurse' in many headings.

One possible way to investigate whether the new QRD template increases patient comprehension or not is to use a readability test involving package leaflets written according to the QRD template version 8 or its predecessor. A crossover comprehensibility test as described by Fuchs in the PAINT 1 study [23] is a feasible method for use in this study.

4.3. Development of test package leaflets for a commonly used active ingredient

In an initial step, package leaflets for a commonly used active ingredient will be designed according to either version 7 of the QRD template or the newly published version 8. For each version of the template, a package leaflet in English and German will be produced. The same layout design and type face is considered to be important for both versions in either country to enable a more uniform comparison. It will be attempted to optimise the package leaflet in terms of readability and suggestions from the readability guideline [23] will be implemented e.g. use of bold type face for headings, multiple levels of headings where complex information has to be communicated, lay terms for complicated medical terminology, short sentences and lists with bullet points. An active writing style will be used rather than passive, for example 'take 1 tablet' rather than '1 tablet should be taken'. Advice contained in the template to make a package leaflet more patient friendly will also be put into practice, for example, using commonly used terms for parts of the body rather than system organ classes.

4.4. Development of questionnaires for the readability test

After the package leaflets have been designed, preparation will take place for the readability test in the form of development of a questionnaire in English and German which can be applied to both versions of the package leaflet i.e. that written according to QRD template version 7.3.1 or version 8. In an initial step, the sections of the package leaflet will be prioritised according to their relative importance to ensure safe and proper use of the product. The test questions should demonstrate that the user can locate information in the leaflet, understand it and know how to act on it [43]. Questions will be generated for the different sections and then the content of the expected answer will be decided on. The questionnaires will include a minimum of 15 questions relating to the key safety messages contained in the package leaflet.

Additional general questions concerning the participants' opinions such as the comprehensibility of the package leaflet in general, legibility, and ease of finding information will also be included.

4.5. Pilot test

A pilot test will be carried out in each country of varying educational levels and age, not involving the participants who will be included in the final test. This will show if adjustments, such as in the questionnaire, are required before the main test. The pilot test will also show if the method is suitable for the project.

4.6. Recruiting and questioning participants

The performance based written readability test will be used following recruitment of participants in Germany and England. Where possible a wide range of different ages will be involved resulting in a group of participants which is similar in both countries. As recommended in the Readability Guideline [35], people involved in medicines such as doctors, nurses and pharmacists should be excluded from the test persons, younger as well as older people will be included as well as new users. All participants will receive an explanation of the test and the procedure and should answer a few basic demographic questions regarding age, gender, education and whether they take any medicines at the present time. In the study, the people taking part will be given the package leaflet for a commonly used active ingredient prepared either according to version 7.3.1 or 8 of the QRD template and the questionnaire. Following a wash out period the same participants will then be presented with the alternate package leaflet and same questionnaire. This method of testing has been chosen as it reflects more the real life situation where a patient returns home with a new medicine and reads the package leaflet alone for the first time. Not using an interviewer also means that gestures or mimic from the interviewer cannot influence the answers. It does however therefore rely on the participants possessing certain writing skills and care must be taken in the selection process to ensure that participants with lower writing skills are not excluded.

4.7. Data entry and analysis of obtained results

Speed of finding as well as comprehension are aspects to measure in the planned investigation. The data generated will be coded for example using a SPSS program. Statistical analysis of the results will then be carried out. Results for both versions of the QRD template in the United Kingdom and Germany will be compared to elucidate whether differences are seen between the countries. The subjects' personal opinions will also be analysed for both templates.

5. Literature

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