Key (Safety) Information in Readability User Testings

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Preamble

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List of Abbreviations

API	Active Product Ingredient
AR	Adverse Reaction
CA	Competent Authority
CMC	Chemistry Manufacturing and Controls
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CRO	Contract Research Organisation
CSM	Committee on Safety of Medicines
CTD	Common Technical Document
EC	European Commission
EMA	European Medicines Agency
EU	European Union
IMP	Investigational Medicinal Product
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
PIL	Patient Information Leaflet
PL	Package Leaflet
OTC	Over-the-Counter; in this context: Medicines that are sold directly to a consumer without a prescription from a healthcare professional
QRD	Quality Review of Documents
SmPC	Summary of Products Characteristics
UK	United Kingdom

1 Introduction and Purpose

All medicinal products are required by *Article 54, Article 55 and Article 59 of Directive 2001/83/EC as amended* to be accompanied by outer/inner labelling text and a package leaflet setting out comprehensive information which is accessible to and understandable by those who receive it, so that they can use their medicine safely and appropriately. The safe and correct use of all medicines depends on users reading the labelling and packaging carefully and accurately and being able to understand and act on the information presented.

Article 63(2) of Directive 2001/83/EC requires also 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 package leaflet must be clearly legible in the official language or languages of the Member State(s) in which the medicinal product is placed on the market.

Article 59(3) of Directive 2001/83/EC provides that the package leaflet shall reflect the results of consultations with target patient groups to ensure the requirements of *Article 63(2)* are met.

The topics of this masterwork are:

- To investigate the importance of "key (safety) information" for the submission of readability user testings via a questionnaire
- To evaluate the background information on regulatory submissions of readability user testings
- To study how colleagues define the expression "key (safety) information" in their daily regulatory practice and
- To investigate on further importance of this term with regard to current ongoing discussions in the regulatory environment.

Furthermore, the goal is to elaborate a definition of the term "key (safety) information" and recommendations for the pharmaceutical industry how to handle "key (safety) information" in readability user testing appropriately considering both the results from the questionnaire and the available guidance documents.

2 Legal Basis

2.1 European Legal Requirement of User Testings

The *EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use (Rev. Jan 2009)* provides the following information:

According to *Articles 59(3)* and *61(1)* of *Directive 2001/83/EC as amended by Directive 2004/27/EC* new requirements apply to the package leaflet. *Article 59(3) as amended* requires that consultation with target patient groups be carried out to demonstrate the readability and usefulness of the package leaflet to patients.

Article 59(3) reads:

"The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use."

Article 61(1) states that:

"*The results of assessments carried out in cooperation with target patient groups shall also be provided to the Competent Authority.*"

Article 63(2) states 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."

In addition, *Article 28(2)* and *(3)* of *Directive 2001/83/EC* require that products authorised through the Mutual Recognition and Decentralised Procedures will result in a harmonised package leaflet between Member States. From my opinion, this reflects also the growing importance of fulfilling the updated requirements on package leaflets and the related user tests.

Further information is given in *EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use (Rev. Jan 2009)*:

The requirements apply to the PL for all marketing authorisations granted after 30 October 2005. Therefore all package leaflets included in a marketing authorisation application have to be checked accordingly, and the report summarising the result of consultation with target patient groups must be included in the CTD dossier, Module 1.3.4.

Additionally, it is essential to perform the user testing or another justified consultation method before granting or varying any marketing authorisation, independently if the product falls under Centralised, Mutual Recognition, Decentralised or national procedures.

Further to that, all regulatory Competent Authorities (Member States and the European Medicines Agency) agreed on harmonised Quality Review of Documents (QRD) templates for the package leaflet to ensure that the statutory information appears as intended by the *Directive 2001/83/EC.*

Compliance with the QRD templates is mandatory but does not exempt from the obligation to perform a user test.

Further to the **first authorisation of a medicinal product,** in the following situations a user consultation is always required:

- Medicinal products which have undergone a **change in legal status**
- Medicinal products with a **new presentation**
- Medicinal products with **particular critical safety issues**

For changes to existing marketing authorisations, the need for user consultation covers in principle situations where **significant changes** are made to the package leaflet, either through a variation or a procedure according to *Article 61(3)* of *Directive 2001/83/EC.*

In the *"Readability Guideline"* the following **assessment criteria** are listed for Competent Authorities' approvals of package leaflets related to the consultations submitted in support of a package leaflet:

- Data gathered from users under defined conditions
- The people who are likely to rely on the package leaflet for a particular medicine will depend upon a number of factors and may include carers (e.g. parents, partners, friends, as well as nursing assistants) rather than patients if the medicine is generally intended for administration by someone other than the patient.
- In order to ensure that those involved can understand and apply the information, the evidence presented must demonstrate that they can pick out the relevant information, interpret this and describe the action they would take as a result.
- The **key information** will need to be defined prior to the consultation by the marketing authorisation holder and is likely to include significant side effects, warnings, what the medicine is for and how to take/use the product.

2.2 United Kingdom's Legal Requirement of User Testings

Even before the European requirement entered into force, the United Kingdom (UK) made user tested package leaflets mandatory for all new applications for marketing authorisations with the due date 1 July 2005, including all package leaflets currently on the market.

As outlined in *MHRA's Guidance on the User Testing of Patient Information Leaflets (Jun 2005)* the following implementation constraints applied to this new requirement:

- All applications which include a PL and are submitted for assessment to the MHRA will be considered against criteria defined in the guidance
- The guidance affects all new applications for marketing authorisations (MAs) submitted on or after 1 July 2005 applying in all areas of MHRA work (incl. e.g. herbals)

- Final date for all leaflets to comply with requirements to reflect user testing and the changes in the order of the information presented: By 1 July 2008 - following a transitional period for existing MAs
- Possible exemptions of the requirement are furthermore listed - appropriate justification must be provided by the applicant

For two reasons a boom of user testing companies in the UK occurred:

- Most of the European marketing authorisation holders (MAHs) prefer to perform user tests on their English written leaflets
- The local national obligation applying for UK MAHs

2.3 Legal Basis for Bridging Reports

According to the *"Readability Guideline"* full user test is not mandatory under all circumstances, instead evidence from tests on similar package leaflets may be used where appropriate.

It may be appropriate for an applicant or MAH to refer to a representative sample of PLs for medicinal products which comply with these legislative requirements. The types of package leaflets should be chosen carefully to be representative, e.g. recently approved PLs for a corresponding medicinal product.

Examples of when this may be acceptable based on an appropriate justification are:

- Same safety issues identified
- Same class of medicinal product
- Extensions for the same route of administration e.g. intravenous/intramuscular

However, certain package leaflets may require further user consultation to provide reassurance that patients benefit from the information provided. This is e.g. the case where user consultation concentrates on one particular aspect of a leaflet which may need particular patient attention, e.g. expression of risk of side effects. These are the so called "focus tests".

CMDh/100/2007, Consultation with Target Patient Groups - Meeting the Requirements of Article 59(3) without the Need for a Full Test - Recommendations for Bridging (Rev. Apr 2009) gives further recommendations:

In bridging, a successful user test on one (1) package leaflet [the "parent" PL] can be used to support a justification for not testing other similar leaflets ["daughter" PLs]. In some circumstances it may be appropriate for some "daughter" PLs to bridge not only to the results of testing for only one "parent" PL, e.g. possibility to refer to the design and layout of one (1) PL and to the content of the leaflet for an other product.

Since the design and layout of the information is crucial to how the information is used and understood, "daughter" PLs should be of the same design, layout and writing style as the "parent" PL in order for bridging to be successful. A bridging proposal is unlikely to be acceptable to the Competent Authority where this concept has not been adhered to.

The principle of preparing bridging reports is further described in *MHRA's Guidance for the Pharmaceutical Industry on the Use of BRIDGING STUDIES to Demonstrate Compliance with Article 59(3) of Council Directive 2001/83/EC [Consultation with Target Patient Groups](Dec 2006):*

"Bridging will normally be acceptable for PILs for medicines in the same therapeutic class where the clinical information set out in the Summary of Product Characteristics (and therefore the information in the PIL) is similar.

Importantly the key messages for safe use with the related medicines should be similar."

2.4 Key (Safety) Information – Legal Definition

Is there a legal definition/legal basis for the terms "key safety messages", "key information", "key (safety) information"?

There is neither a clear definition nor a law to be retrieved. There is only the following information available in guidance documents ("soft law"):

EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use (Rev. Jan 2009) as well as the ***MHRA Guidance on the User Testing of Patient Information Leaflets (Jun 2005)*** state that the key information **needs to be defined by the MAH** prior to the user testing and is likely to include

- Significant side effects
- Warnings
- Indications
- How to take/use the product

The *Annexes* of the above mentioned documents offer further information:

- Questions should reflect **specific issues for safe and effective use**
- Avoiding **serious safety issues** would invalidate the user testing
- Questions should adequately cover any **critical safety issues** with the medicine
- Questions should be kept to a minimum (usually 12 -15 will be enough), though more may be required in special cases, e.g. if there are **significant safety issues** to be investigated
- Questionnaire within the protocol will have to address the **key messages** and provide evidence that these messages can be found and understood so that the medicine can be used safely

Further to that ***CMDh/100/2007, Consultation with Target Patient Groups - Meeting the Requirements of Article 59(3) without the Need for a Full Test - Recommendations for Bridging (Rev. Apr 2009)*** stresses the importance of key (safety) information in the frame of bridging reports:

- Successful user consultation will have identified up-front the **key messages for safe use** with particular medicine in question
- For each medicine these **messages** will be different although the leaflet will cover the same sort of information

- Questionnaire within the protocol submitted with the application for the "parent" PL
    - Have to address these **key messages**
    - Provide evidence that users can find and understand these messages and act appropriately so that the medicine c**an be used safely**
- Bridging report submitted for the "daughter" PL the **key messages for safe use** for both the "parent" and "daughter" PLs need not be identical

With well defined key (safety) information bridging will be eased when:

- K**ey messages for safe use** identified for a range of medicines are similar and the PLs are designed, laid out and written in an identical manner
- **Key messages for safe use** needed to be discussed first of all the within the "daughter" PL and justify how these are covered within the test carried out on the "parent" PL; in cases without **identical key messages** (and this will apply to many bridged PLs) the bridging report will need to critically appraise these differences and address the relevance of the questionnaire to the "daughter" PL.; synergies and similarities in the **key information** should be discussed.

In its guidance document ***Always Read the Leaflet: Getting the Best Information with Every Medicine (Jul 2005)***, MHRA's CSM Working Group on Patient Information elaborated the concept of "headlines" containing key safety information and warnings about use of a medicinal product that a patient needs to be aware of at the start of therapy. This guideline is not concerned with user testings but nevertheless provides information about the presentation of key messages in the PL. In order to improve the quality of the package leaflet, the **key information on the safe and appropriate use** should be presented as concise "key information" headline section at the start of the PL and using a larger font size. The information should be presented in two (2) to six (6) bullet points but the length is not fixed and may differ. The section should be kept short, it should not be considered as substitute for reading the entire PL.

In general, it should be the *"**most essential messages**, bearing in mind the product and its context"*. In the following, this guidance documents offers suitable types of information which should be included:

- Why the patient should take the product
- The maximum dose or duration of treatment
- Potential side effects/withdrawal reactions (symptoms to look out for, especially for common or serious side effects)
- Contraindications
- Important drug interactions
- Circumstances in which the drug should be stopped
- What to do if the medicine doesn't work
- Where to find further information

Furthermore, a list of types of issues considered as less suitable for the headline section is provided:

- Hypersensitivity (which is almost universally listed as a contraindication) except where it is a significant clinical issue e.g. penicillin.
- Contraindications in uncommon conditions – specifically those which the patients would be expected to be aware of if they have the condition e.g. porphyria.
- Precautions, that are primarily relevant for the doctor's decision on whether to prescribe. For example, psychoactive drugs that should be prescribed with caution to patients with a history of drug abuse.
- Strict advice to avoid a medicine during pregnancy or lactation should only be included in the headline section if there are important safety data to support this recommendation.
- Undesirable effects and interactions that represent issues of tolerability rather than of safety (e.g. gastrointestinal upset, headache), or are unlikely to be of major clinical importance.
- Advice relating to rare scenarios in which the patient would seek urgent advice (e.g. stroke, anaphylaxis, a first seizure) and where the advice in the PL headline section would be unlikely to have any bearing on the action taken by the patient.
- Overdose, unless there is a particular concern e.g. paracetamol.

For the sample of this headline concept for key safety messages provided in ***Always Read the Leaflet***, please refer to Table 1.

Important things that you need to know about [PRODUCT]: • Your doctor has prescribed [PRODUCT] because it is a treatment for X. • If you are pregnant or could get pregnant you should talk to your doctor before taking [PRODUCT]. • Taking some other medicines with [PRODUCT] can cause problems. Tell your doctor if you are taking anything else (including herbal or "natural" remedies). If you are, you should read the section below on "taking other medicines" carefully. • Do not take more than 4 tablets in 24 hours. • Do not stop taking this medicine suddenly – you might get a reaction, such as… • Most people don't get side effects taking [PRODUCT] but some people do – for example inflammation of the liver (hepatitis): see page 2 for more information. **Now read the rest of this leaflet.** It includes other important information on the safe and effective use of this medicine that might be especially important for you. **This leaflet was last updated on xx/xx/xx**

Table 1: Sample of Headline Concept

The expression "key (safety) information" must be identified by the marketing authorisation holder/agency case by case for each medicinal product. For every compound its specifically important key safety messages should be previously defined and addressed in the user testing questionnaire.

In conclusion, a definition of “key (safety) information” is paraphrased in a complex way and spread over many text passages in several legal guidance documents, but no compiled definition is given. In this section all information available in those documents was gathered. The target of this master thesis is to elaborate a definition of “key (safety) information” from the regulatory guidance documents as well as from the survey conducted, please refer to section 5.2 Defining Key (Safety) Information in Daily Practice.

Regarding the name of the term used for “key (safety) information” various expressions can be found in the above provided available regulatory documents:

- “Key messages for safe use”
- “Key information”
- “Serious/critical safety issues”
- “Key messages”
- “Specific issues for safe and effective use”
- “Headline information”
- ...

For the purpose of this master thesis, the expression “key (safety) information” is used to summarise all of these terms.

3 Methods

3.1 Questionnaire

3.1.1 Introduction

In order to evaluate how pharmaceutical companies define „key (safety) information“ in their daily practice, a survey was conducted via a questionnaire sent out to approximately 200 colleagues working in Regulatory Affairs throughout Europe (for details see 4.1 General).

3.1.2 Development

To develop an understandable and clear questionnaire and to avoid misunderstanding of the questions as much as possible, a pilot questionnaire was used – equivalent to what is outlined in the guidance documents for questionnaires of user testings, too.

The pilot questionnaire was sent to ten (10) subjects, from whose six (6) completed pilots were received. The subjects were requested to fill out the questionnaire as well as comment on its comprehension and clarity.

Based on these results, the following revisions of the questionnaire were performed:

- Question 2 and Question 9: More clarity via cross-reference to previous Questions 1 and 5
- Question 3: Acceptance of user tests by Competent Authorities: Three further possibilities were added in order to cover pending procedures. Furthermore, non-acceptance was sub-classified into “rejection” and “deficiencies”
- Question 4: Reasons for requirement of user testings: Free text response was added as the catalogue seemed not to be complete
- Question 8: Classification of content of PL as key (safety) information): Three (3) options instead of one (1) for choice: “YES – in any case”, “YES – depending on medicinal product”, “NO”. This was done in order to receive a wider range of information on this main target of the questionnaire

For motivation purposes smiley graphics were incorporated, too.

For a sample of the pilot questionnaire, please refer to Annex 1.

3.1.3 Content and Structure

Questions addressed to the participants:

1. How many readability user testings have you already submitted to an agency?
2. How many of the testings of question 1 have been bridging reports?
3. Have these testings (incl. bridging reports) been accepted without deficiencies?
4. What was/were the reason(s) for the requirement of your user testings (incl. bridging reports) for your medicinal product(s)?

5. How have your user testings (incl. bridging reports) been conducted?
6. Acceptance by agencies per parties performing the user testings (incl. bridging reports)
7. Readability user testings are focused on the key information/key safety information of a medicinal product. How do you define "key information/key safety information" in your own words?
8. Which of the following would you classify as key information/key safety information for a questionnaire of a user testing?
9. How did you ensure that the key information/key safety information for your medicinal product has been covered by the questionnaire of the user testings (incl. bridging reports)?
10. What parties have you involved/would you involve in defining the key information/key safety information of a medicinal product?
11. With the EU pharma package the EU commission targets to inform patients about the key information of medicinal products. Are you aware of these plans?
12. The new "Guideline on Summary of Products Characteristics" as of September 2009 asks to summarise the key safety information in section "4.8 Undesirable effects" / subsections "a. Summary of the safety profile" and "c. Description of selected adverse reactions". Are you aware of this requirement to be implemented in May 2010?
13. Your personal comments

Table 2: List of Questions

The questionnaire was structured into four (4) parts:

1. **Background information on user testing submissions and their acceptance** (Question 1 to 6 and Question 9)
    - Question 1: Number of user testings submitted to agencies (in total)
    - Question 2: Number of bridging tests
    - Question 3: Acceptance by agencies with different categories
    - Question 4: Reasons for requirement of a user test (incl. bridgings)
    - Question 5: Parties conducting the user testings (incl. bridgings)
    - Question 6: Acceptance by agencies broken down per conducting parties
    - Question 9: How to ensure that key (safety) information was covered by parties conducting the tests
2. **Personal definition of key (safety) information in user testings by attendees** (Question 7, 8 and 10)
    - Question 7: Definition of expression "key (safety) information" in their own words
    - Question 8: Based on the structure of the PL following QRD templates, the attendees were asked to decide whether they would classify each of the different sections of the PL as key (safety) information for user testings. Possible answers were:
        - YES – in any case
        - YES – depending on the medicinal product
        - NO

Furthermore, the attendees had the possibility to comment on their decision.

- Question 10: Parties that (would) have been involved to define key (safety) information by the attendee

3. **Current discussions - Key (safety) information** (Question 11 and 12)

- Question 11: Awareness of EU Pharma Package targeting to inform patients about the key information of medicinal products
- Question 12: Awareness of *"SmPC Guideline" (Rev. September 2009)* new requirement to summarise the key (safety) information in section "4.8 Undesirable effects" / subsections "a. Summary of the safety profile" and "c. Description of selected adverse reactions".

4. **Room for personal comments** (Question 13)

For a full sample of the questionnaire please refer to Annex 2.

As this master thesis is focussed on the key (safety) information in user testings and not only user testings in general, attendees were encouraged to send their questionnaires back even if they had no experience in user testings / submission of user testings. Consequently, these responders were asked to come back with questionnaires only completed with responses on Questions 7, 8, 10, 11, 12 - equivalent to 2. and 3. above. No experience was defined as zero (0) user testings performed / submitted.

Note: The written English comments by participants were copied and pasted into section 4 Results and Annex 3. However, some typos and grammatical mistakes were corrected when absolutely necessary for comprehension. One participant answered in German, these comments were translated into English. The abbreviations used in the comments by the participants are explained in section List of Abbreviations.

4 Results

4.1 General

Sixty (60) responses on the final questionnaire have been received for evaluation and discussion within this master thesis. Most of them were received from colleagues of Germany, and some from Austria, the United Kingdom, Ireland, Benelux, France, Nordic countries, Greece, Spain and Italy. The majority is employed in the pharmaceutical industry, some in regulatory consultant's offices, working on human as well as veterinary medicinal products; generic and originator's companies are represented.

Half of the responders (30) had experience with user testing submissions.

4.2 Background Information on Submitted User Testings

The thirty (30) attendees having already performed/submitted user tests were requested to complete the entire questionnaire. In total, 146 user testings have been submitted to Competent Authorities (CAs).

4.2.1 Ratio Full User Testings / Bridging Reports

Out of 146 user testings submitted, 46 (32%) were bridging reports and 100 (68%) were full tests. For further background information on bridging, please refer to 2.3 Legal Basis for Bridging Reports.

4.2.2 Reasons for the Conduction of User Testings

There are specific reasons given in the available guidance documents when a user testing is mandatory to be conducted and submitted in the frame of regulatory submissions – see 2.1 European Legal Requirement of User Testings.

Questions 4 evaluated the reasons for submission of readability user testings and was structured according to the legal basis as outlined in the *EC Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use, Chapt. 3/4. (Rev. Jan 2009)* - see also 2.1 European Legal Requirement of User Testings. Six (6) options could be selected of which two (2) provided the possibility of free text response. The attendees of the questionnaire named a broad range of legal reasons, mostly in line with these categories (see also Figure 1):

- The majority of user testings was performed in relation to **first marketing authorisation application** of a medicinal product (43%). Further details were given for two (2) tests conducted for a marketing authorisation application with known substance, two (2) with unknown substances and one (1) for a combination of two (2) known substances.

- 12% were conducted due to "**other significant text changes**". Most of them (10%) were due to the harmonisation of package leaflet/label, 1% due to update to QRD format and 1% for a legacy product information (no PL available) for which it was legally required to create a package leaflet.
- **Medicinal product with a new presentation** was the basis for 6% of the user testings.
- 2% were created because of a change of the PL due **to particular critical safety issues**.
- The minority was due to a **change in the legal status** of the medicine (1%).

Furthermore, when selecting the option "other reasons" the participants could provide further details in free text. These were:

- **Renewal** (10%): Renewal applications are also often related to a harmonisation of the PL/label as well as QRD updates. Therefore, this option partly overlapped with the option "other significant text changes".
- **Local national requirement** (25%): These tests were performed for medicinal products licensed in the United Kingdom – for background information please refer to 2.2 United Kingdom's Legal Requirement of User Testings.
- **Layout changes** (1%): Specifically, the switch to landscape format was mentioned here.

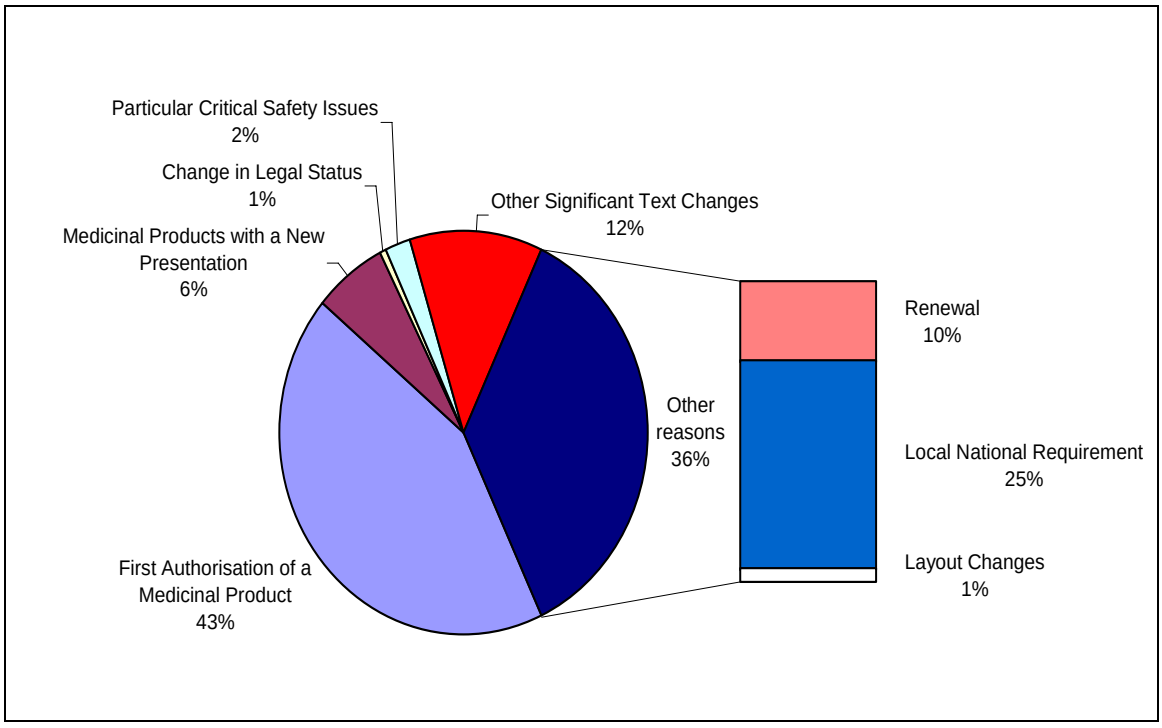

Figure 1: Reasons for the Conduction of User Testings

4.2.3 Acceptance of User Testings by Competent Authorities

The acceptance by Competent Authorities of the submitted user testings (including bridging reports) was extremely high: 65 % were **approved without** any **deficiencies** and none was **rejected**.

This percentage is even higher if one excludes the pretty high number of testings which is currently under assessment and no feedback has been received, yet. This calculation would lead to 81% of testings approved without any deficiencies.

Additionally, 12% were **accepted although weaknesses** were identified.

For the **pending procedures**, 3% received a deficiency letter, 1% a positive pre-assessment and for 19% no feedback was received by the day of completion of the questionnaire – see Figure 2.

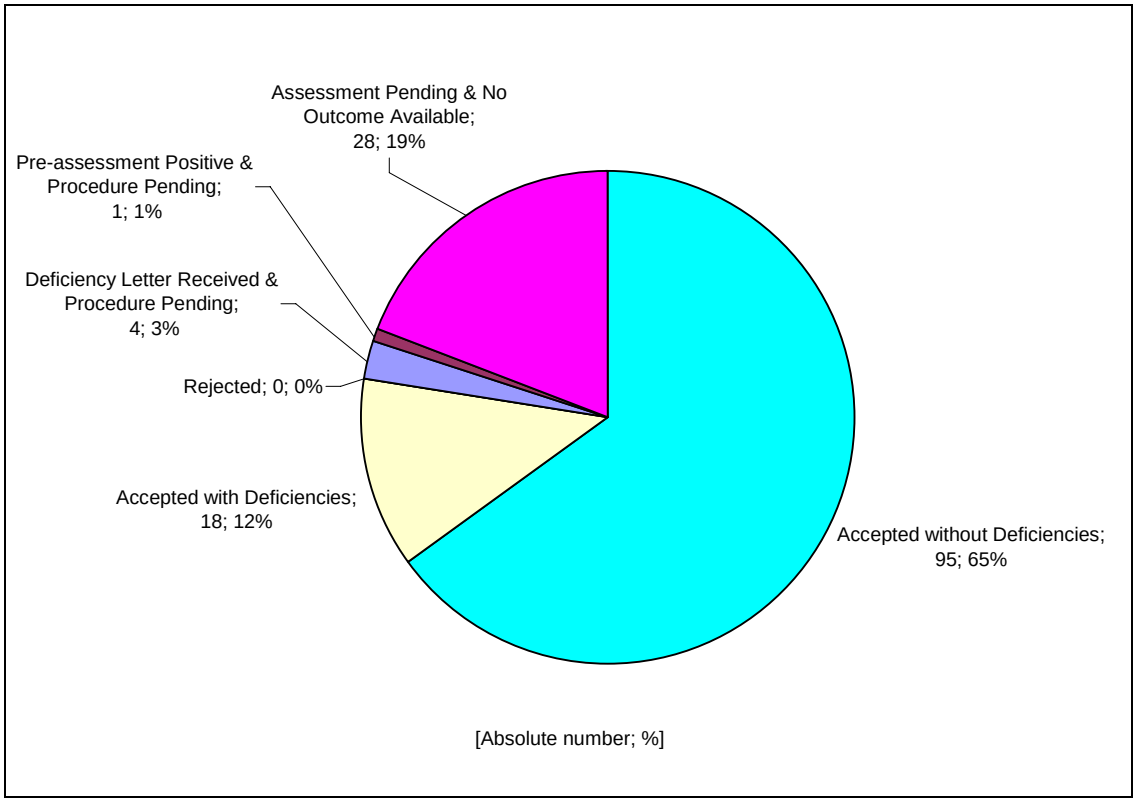

Figure 2: Acceptance of User Testings by Competent Authorities

Most of the weaknesses were caused by wording issues, especially with regard to patient-friendly wording but also due to redundancy and content.

Furthermore, inconsistencies with SmPC or labelling were detected. In one case, during the assessment of the user testing one missing class contraindication in the product information was identified to be updated via type II variation.

Protocol deficiencies were given, too. These were for example: Missing demographic data of participants; missing justification why only one version of the package leaflet was submitted, in which the deficiencies in readability and comprehensibility detected within the scope of the readability testing have not been resolved.

Additionally, requests on the layout like emboldening of key messages, use of bullets instead of prose, non-use of underlining italics etc. were raised.

Surprisingly, only twice deficiencies related to key (safety) information were given:

- "Key safety messages were not identified up front, and as a result, the questions asked to not appear to address these fully."
- "The evaluator at the EMA did not think that the full range of key safety information was covered in the original PL-test-report. Therefore a focus test report was requested by the EMA concerning 2 issues (one from lactation section, one from dosage + admin section)"

For the full list of deficiencies provided by the responders – see Table 3.

List of Deficiencies
• Patient-friendliness missing for some expressions
• Key safety messages were not identified up front, and as a result, the questions asked to not appear to address these fully.
• Frequencies to be worded more patient-friendly
• Discrepancies with SmPC
• Type face: product name should not be in capital letters (undue attention) but italicized and underlining text missing;
• Considering emboldening of key phrases
• Only amendments of content
• The evaluator at the EMA did not think that the full range of key safety information was covered in the original PL-test-report. Therefore a focus test report was requested by the EMA concerning 2 issues (one from lactation section, one from dosage+ admin section)
• User-friendliness of package leaflet should be further improved
• Product name used to often, section that are not applicable should be removed, shorten PIL
• Redundant wording
• Inconsistence between PIL/label
• Protocol weaknesses
• Mainly on the methodology followed
• Readability improvement
• Information in the incorrect place
• Re-phrasing of adverse drug reactions in patient-friendly manner
• Protocol deficiencies (demographic data of participants missing, participant's opinion not considered in formal assessment, no consideration to change presentation of information where participant's had "some difficulty" in finding)
• "Using other medicines": Medicines should be listed in bullets not in prose
• For allergies (section 2) cross-reference to section 6 missing
• Class contraindication is missing in PIL as well as SmPC: To be updated via type II variation
• Typos to be corrected, wording in "taking other medicines" to be shortened, warning on surgeries to be emboldened
• Warnings and adverse events to be added following SmPC content
• Key messages to be emboldened for emphasis
• One adverse event missing compared to SmPC
• Size of leaflet paper to be increased
• Justification why only one version of the package leaflet was submitted, in which the deficiencies in readability and comprehensibility which have been detected within the scope of the readability testing have not been resolved
• Wording needed to be changed to be more and more 'friendly' understandable

Table 3: List of Deficiencies

4.2.4 Parties Performing User Testings

The participants were asked how the user testings (including bridgings) were conducted. The three (3) options were:

1. **Externally** (conducted by consultant specialised on user testings)
2. **Internally** (conducted by company's function/department specialised on user testings)
3. **Other** (e.g. you work at a consultant specialised on user testings)

Most of the testings were performed externally (97%). Only 3% were conducted internally by specialised company's function/department. For two (2) of those four (4) internal ones further information was provided stating that these were bridging reports.

The option "other" was not chosen by anybody.

4.2.5 Acceptance depending on Performing Party

The intention of Question 6 was to compare the performance between the parties conducting the user testings. Only four (4) tests were prepared internally and all of them were accepted without deficiencies or are still under assessment without result available. Based on these little case numbers, a conclusion that 100% of the internal user testings was successful might be incorrect.

Consequentially, the results for the accepted external tests are equivalent to the ones in 4.2.3 Acceptance of User Testings by Competent Authorities.

In conclusion, the purpose of Question 6 to make a rating of the performance between the conducting parties of user tests could not be fulfilled.

4.2.6 Coverage of Key (Safety) Information in User Testings

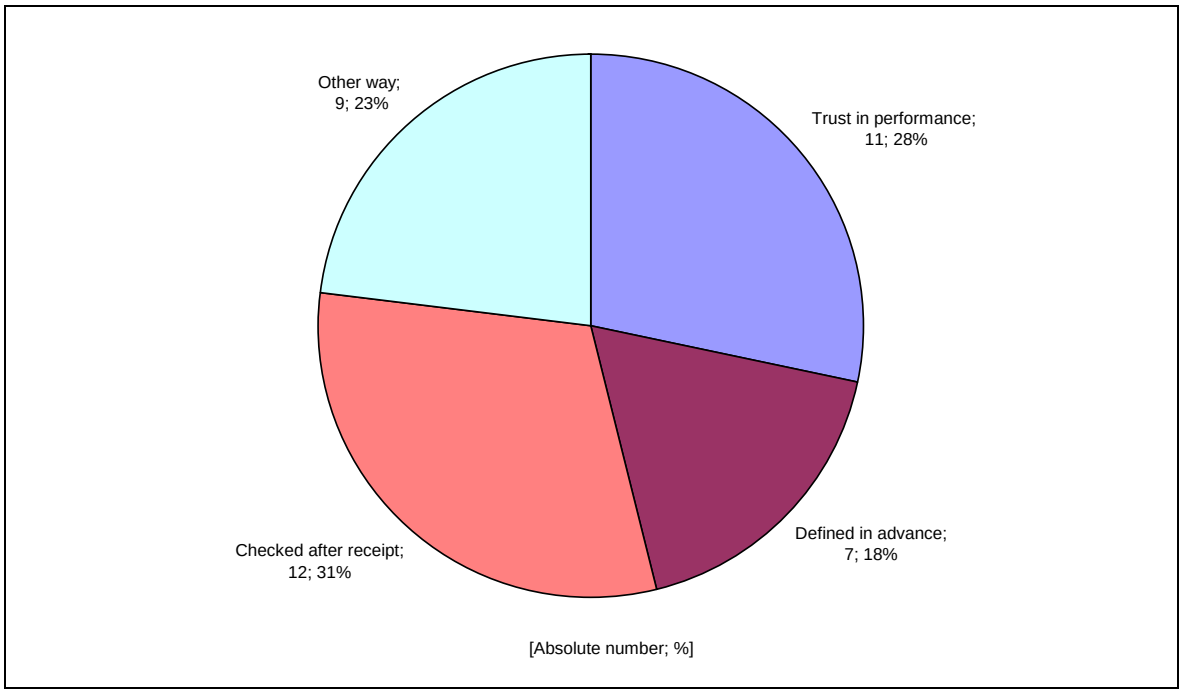

Figure 3: Methods to Ensure Coverage of Key (Safety) Information

Other Ways to Ensure Coverage of Key (Safety) Information in User Testings
• Key information was updated/validated as proposed by the company
• Discussing user testing protocol (and results) with the external company before every testing cycle
• Checked the questionnaire to be used before start of user test that key information in has been covered
• Checked that key information of the questionnaire has been covered before starting the user testing
• Check the proposed questionnaire of the company before the questions are asked.
• Working together with CRO on Questionnaire
• Bridging report - trust in report which have been performed before
• Questionnaire was prepared by external company and checked/reviewed before conducting the test
• The external company defined the key information, we checked before initiate the user testing (validation phase before the user test (PIL - questionnaire…)
• Update/validate the key information as proposed by the company

Table 4: Other Ways to Ensure Coverage of Key (Safety) Information in User Testings

The participants were asked on information how they had ensured that the key (safety) information for their medicinal product was covered by the questionnaire of the user testings (incl. bridging reports). The following possibilities were for choice:

1. **Trust in performance** of the company/function performing the testing
2. **Defined** the key information **in advance** and provided it to the company performing the testing
3. **Checked** that key information has been covered **after receipt** of user testing report
4. **Other way** of ensuring that key information has been covered

   For that point further specification was requested.

Multiple answers were allowed.

To assess possible differences per party preparing the readability user testings, this question was also divided into the three (3) options “externally”, “internally” and “otherwise”– for explanation please refer to 4.2.4 Parties Performing User Testings.

Only four (4) tests were performed internally and none “otherwise”. Therefore, a comparison between the performing parties regarding the coverage of key (safety) information was considered as not meaningful and was therefore omitted – see also 4.2.5 Acceptance depending on Performing Party.

Figure 3 illustrates the following outcome: In total, most of the responders (31%) **checked after receipt** of the user testing reports whether the key (safety) information was covered.

Nearly the same amount (28%) **trusted in the performance** of the party performing the tests and 18% **defined** the key (safety) information **in advance** and provided it to the company performing the testing.

23% (9) of the participants of this questionnaire chose “**other way**” of ensuring that key (safety) messages and most of them (5 of 9 = 13% in total) **checked the coverage** of key (safety) information **in the questionnaire before conduction of the tests**. Two (2) stated that they **up-**

dated/validated the key messages **following the proposal** by the company conducting the readability user testings. One (1) provided information that they worked together with the Contract Research Organisation (CRO). For the details please refer to Table 4.

4.3 Definition of Key (Safety) Information

4.3.1 General

As demonstrated in section 3.1.3 Content and Structure, this master thesis is focussed on the key (safety) information in user testings and attendees without experience in user testings were also encouraged to send their questionnaires back. In contrary to the other responders who completed the form entirely, they were asked to fill out only specific questions like 7, 8, 10 – see the results are presented in sections 4.3.2 and 4.3.3 of this paragraph. Further questions to be completed were Questions 11, 12 and 13 - see 4.4 Current Discussions - Key (Safety) Information and 4.5 Comments by Participants.

4.3.2 Definition in Attendee's Own Words

The purpose of Question 7 was to ask the participants for a definition of key (safety) information in their own words.

Nine (9) attendees of the questionnaire missed to complete this question. Thus the responses of 51 participants were for evaluation.

All answers to this question were compiled and classified into two (2) categories in order to facilitate the review.

1. General Definition of the Term "Key (Safety) Information (68%)
2. General Definition including Examples / PL Sections (32%)

The following samples illustrating the different views were selected:

1. General Definition of the Term "Key (Safety) Information":

- Information crucial for **correct and safe use** of the medicinal product.
- Key information/key safety information are the specific details in the package leaflet which need to be **fully understood** by the patient in a way that he can assess the **risks** associated with taking the medicines in his hands. Consequently, the patient should be able handle the medicinal product appropriately to not expose himself to **risks** exceeding the ones which are outlined in the package leaflet.
- The information within the leaflet (determined by the content of the SmPC and any other useful information on the product/management of the disease) that is considered most key to the patient's understanding of how to **use** the product in a way that:
  1/ minimises any **potential risk** to their **safety**
  and
  2/ maximises the **potential benefit** they will receive from the product.

- I define "key information/key safety information" as the information described in the PIL that needs definitely to be **understood by the patient**.

2. General Definition including Examples / PL Sections:

- The key safety information is the information which contains major details for all users and applicants - independent from level of knowledge. Such information as for example how to use, dosage, warnings, side effects, interactions,.. should be clear and **reader friendly** described.
- Information needed to assess the general safety profile of the product (e.g. possible side effects, interactions etc.)
  Information that is needed for the patient to assess whether the product may be used safely for the particular condition (disease)
  The patient information about what to do and whom to contact in case of any safety-related problems
  Information on how to use the product safely
- Indications/contraindications, warnings, special usage requirements/recommendations, side effects
- The key information/key safety information of the PIL are the domains "area of use" (indication, contraindications, warnings, special patient groups), "adverse events" (side effects, interactions), "dosing" (dosage, application, overdosing, duration of usage), "handling" (expiration, storage).
- Key information: indication, posology/dosing instructions
  Key safety information: contraindications, special warnings, side effects, overdose

For the full list of definitions provided, please refer to Annex 3.

4.3.3 Classification of PL Sections

The participants were asked which of the following sections of the package leaflet they would classify as key (safety) information for a questionnaire of a user testing. The sections presented were those corresponding to the content in the QRD templates but in randomised order.

The following classes were to be selected:

- YES – in any case
- YES – depending on the medicinal product
- NO

Furthermore, comments were possible. These remarks were partly identical for several PL sections.

The following categorisation was carried out by all participants – see Figure 4 and Figure 5:

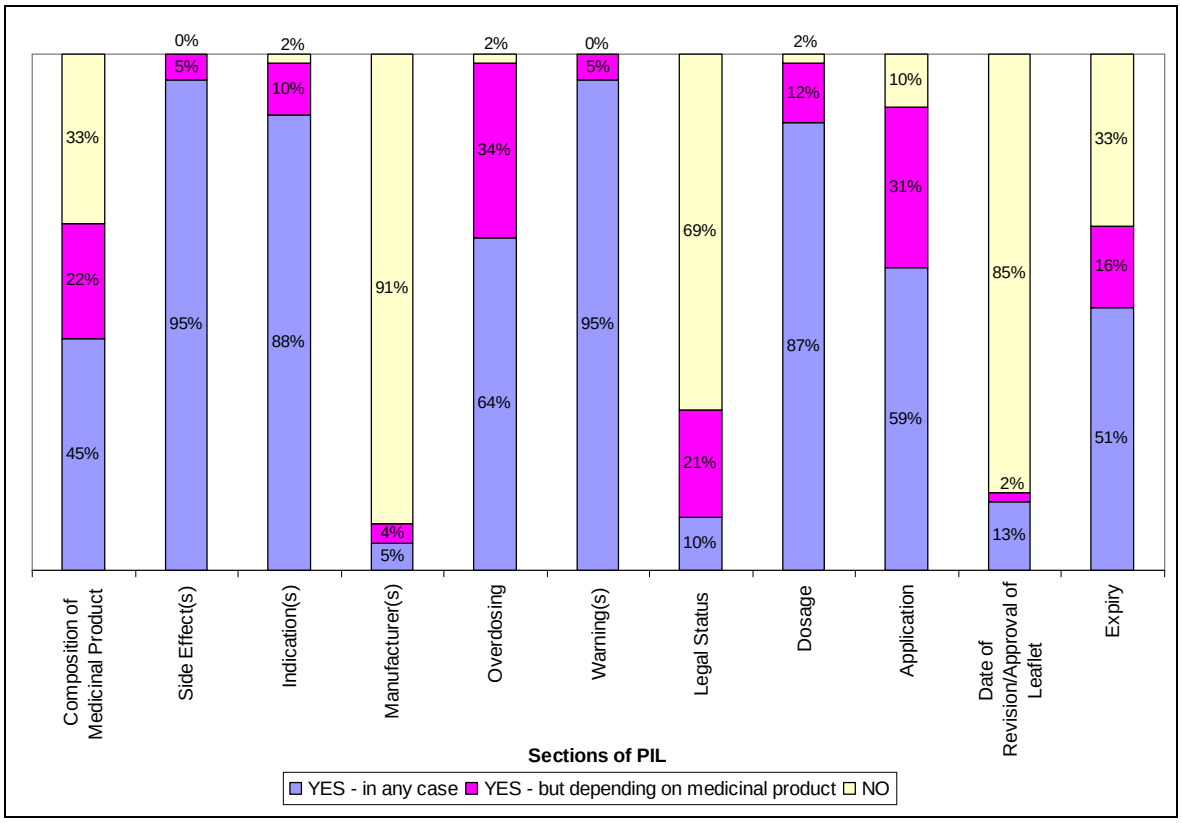

Figure 4: Sections of the PL Classified as Key (Safety) Information I

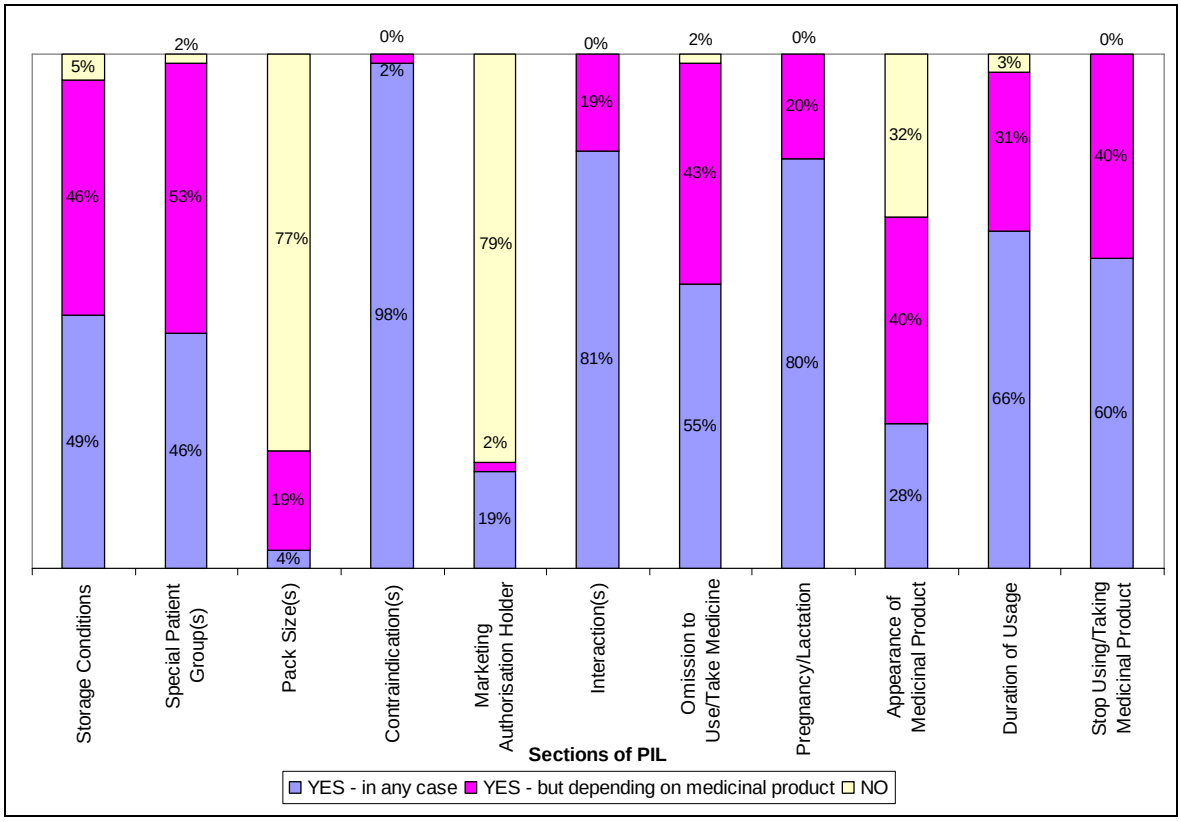

Figure 5: Sections of the PL Classified as Key (Safety) Information II

Further to the general categorisation by all, a subgroup analysis was performed to investigate whether there is a different view by colleagues with experience in readability user testings versus non-experienced colleagues.

“Experienced” participants were considered as colleagues who have performed at least one (1) user test. This subgroup was investigated further:

The maximum of 23 tests was conducted by one attendee, an average of 4.9 tests per experienced participant.

For deeper assessment, the experience was classified into four (4) categories (see Figure 6):

- Performed only one (1) user test: Majority (37%)
- Performed 2 to 5 tests: 33%
- Performed 6 to 10 tests: 17%
- Performed > 10 tests: 13%

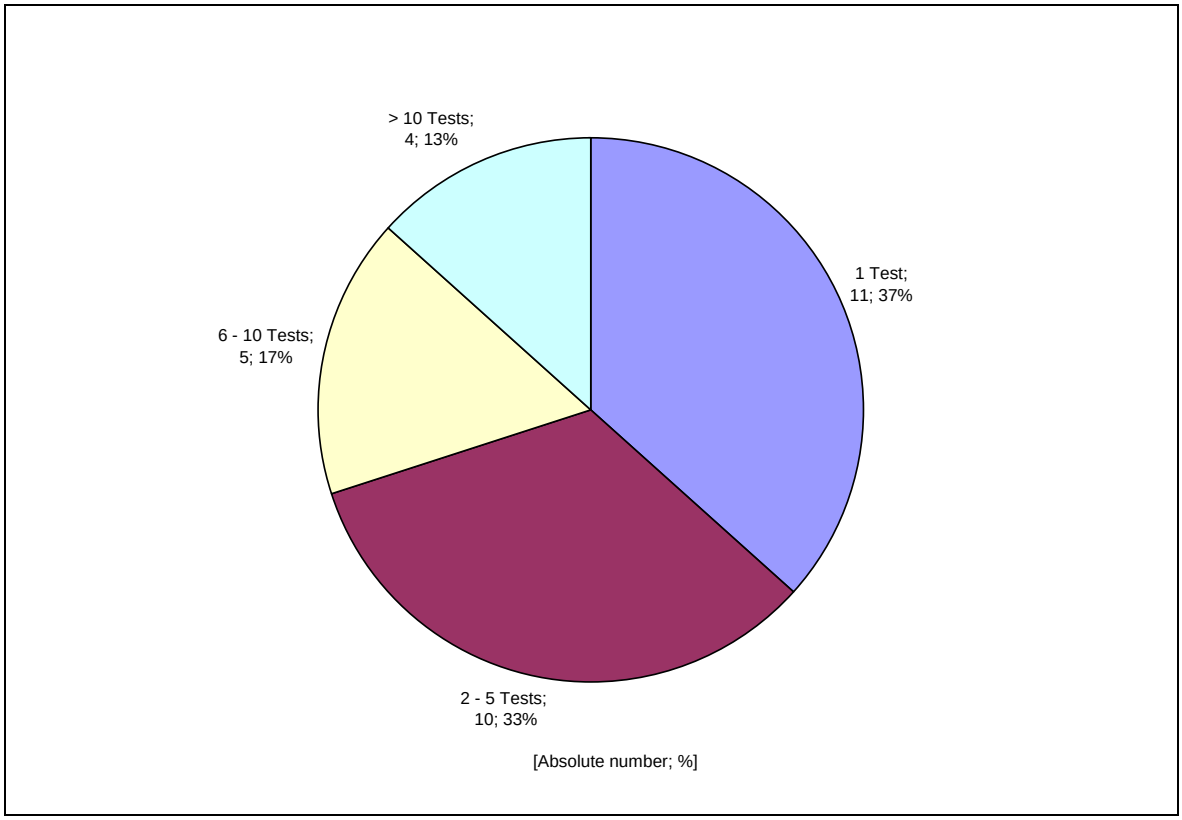

Figure 6: User Tests Performed per Experienced Participant

4.3.3.1 Indication(s)

The majority of the participants decided that the indication should be considered as key (safety) information in user testings in any case – overall percentage 88%. There is also no meaningful dif-

ference in this decision between participants with (93%) and without (83%) user testing experience – see Figure 7.

The following comments were given:

- The patient has to understand what the indication is, particularly for non-prescription drugs
- Depends on type of medication, e.g. when there is off-label use or where the treatment and dosage is different for different indications (e.g. antibiotics) this section might be of high relevance
- Product available without prescription [Remark: This comment was in relation to "YES – but depending on medicinal product"]

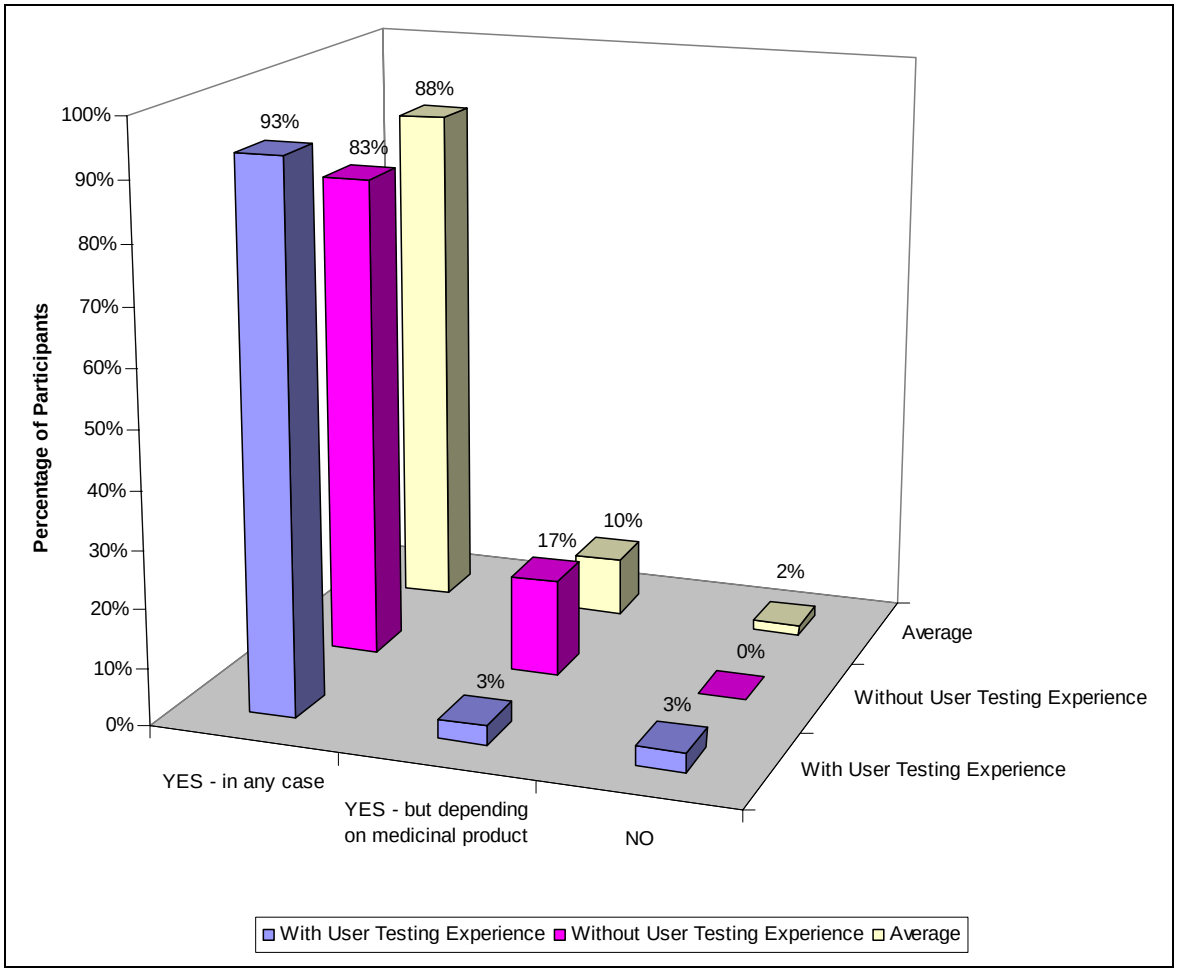

Figure 7: Indication(s) - Considered as Key (Safety) Information

4.3.3.2 Contraindication(s)

An overwhelming unity was shown for contraindication as key (safety) information for readability user testings in any case with a mean of 98% from all participants and also with one tenor from experienced and non-experiences participants (see Figure 8).

The comment provided was:

- Yes, although the physician should have taken this into consideration before prescribing

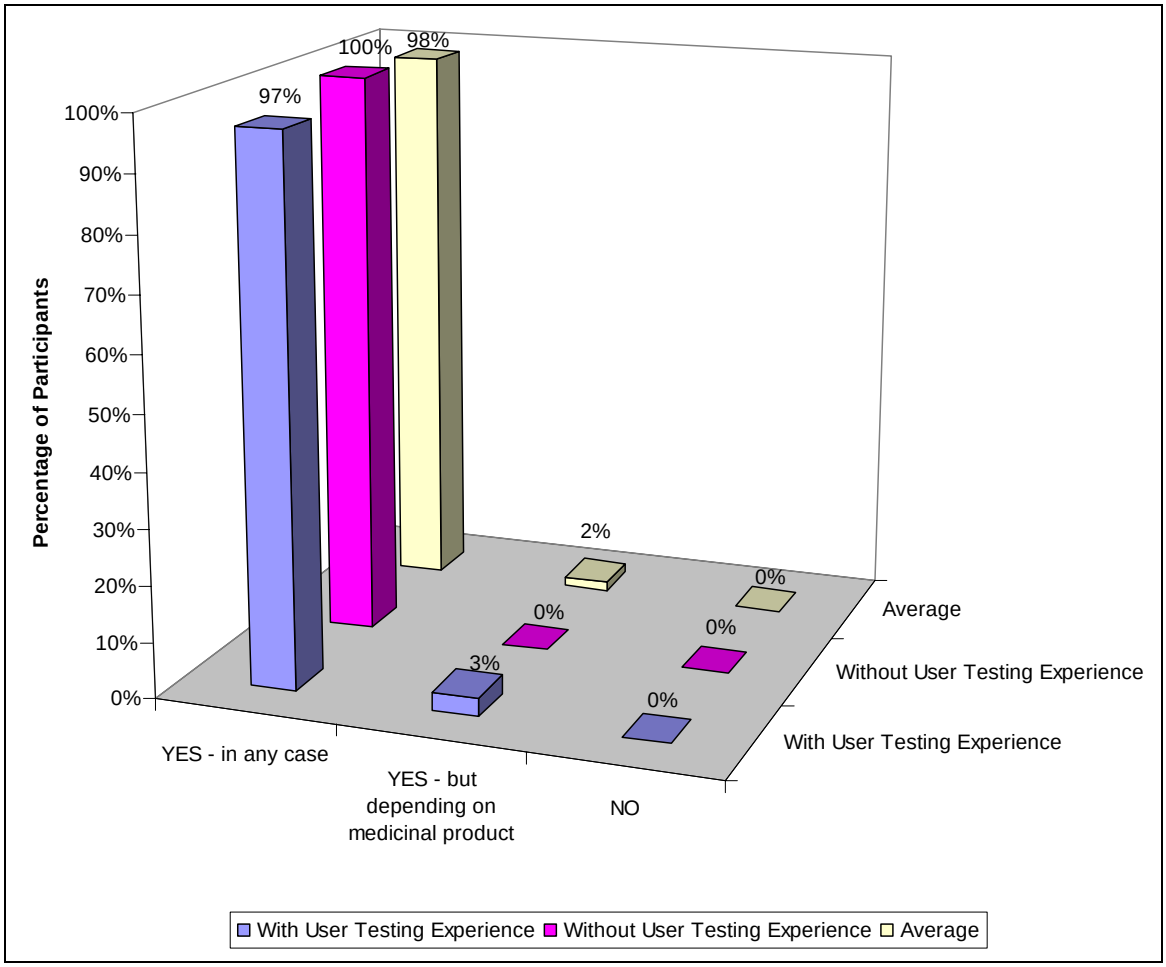

Figure 8: Contraindication(s) - Considered as Key (Safety) Information

4.3.3.3 Warning(s)

As presented in Figure 9, the majority of the colleagues (95% in average) classified warning(s) as key (safety) information for readability user testings with no meaningful difference between participants with or without experience in user testings.

Only one comment was given:

- Should be taken by the physician into consideration

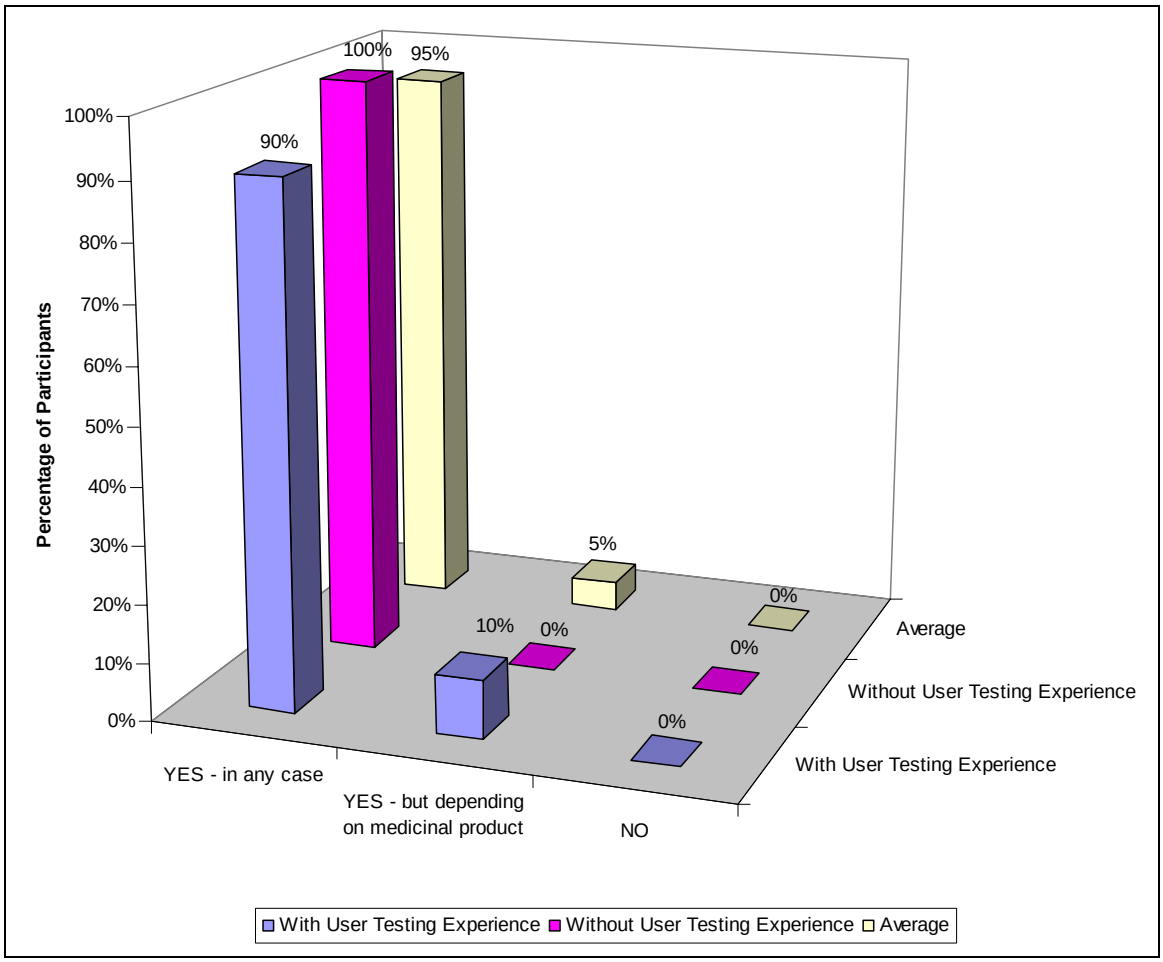

Figure 9: Warning(s) - Considered as Key (Safety) Information

4.3.3.4 Interaction(s)

The majority of 81% considered interaction(s) as key (safety) information in user tests in average. This classification was overwhelmingly chosen by the un-experienced attendees (100%) but by experienced colleagues with much fewer consensus (63%) – see Figure 10.

The comment given was as follows:

- Yes, if there is some specific action necessary

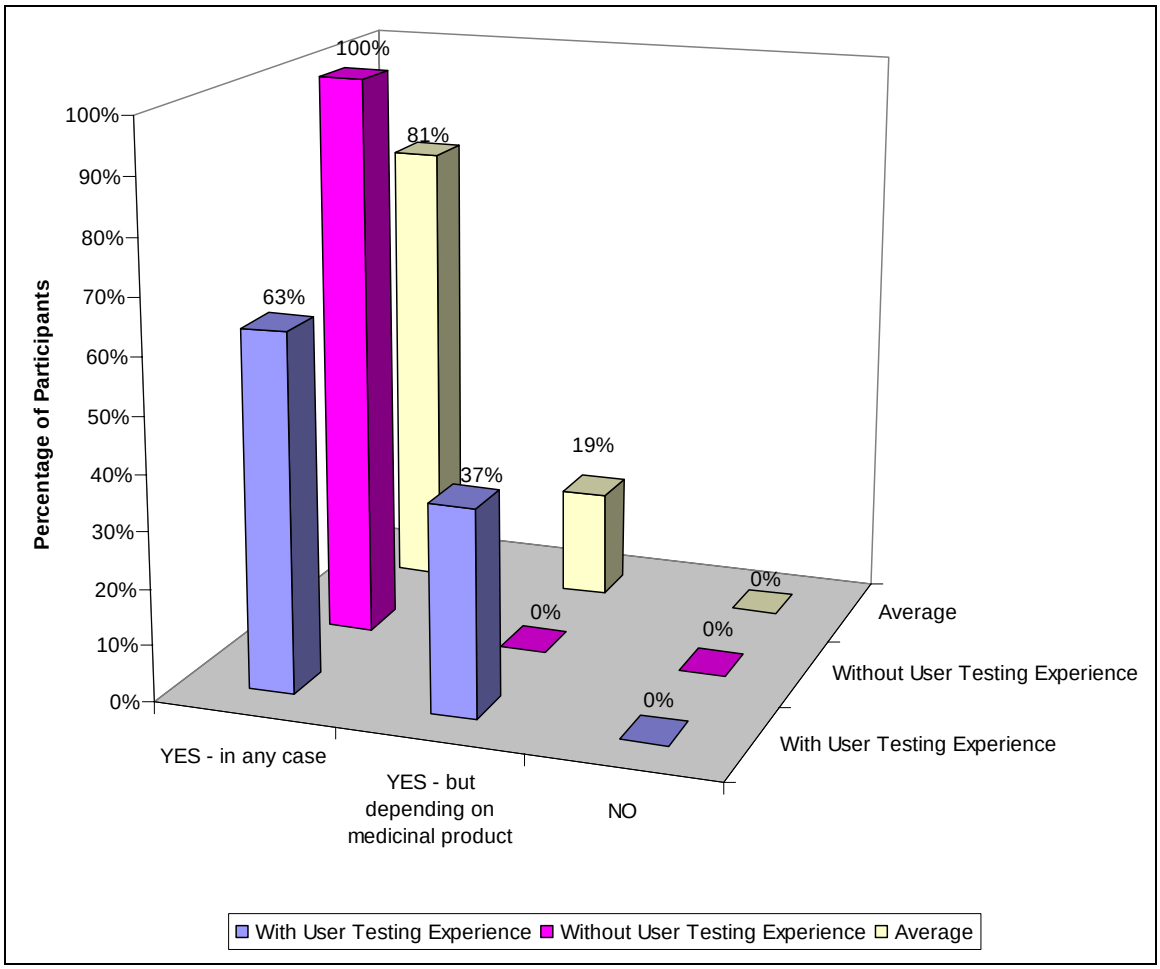

Figure 10: Interaction(s) - Considered as Key (Safety) Information

4.3.3.5 Pregnancy and Lactation

The average of 80% categorised pregnancy and lactation as key (safety) information in readability testings. On one hand 90% of the colleagues without user testing experience made this classification and on the other hand 70% of the ones with experience – see Figure 11.

The following comments were retrieved:

- Yes, if there is some specific action necessary e.g. consultation of physician
- In case of contraindication

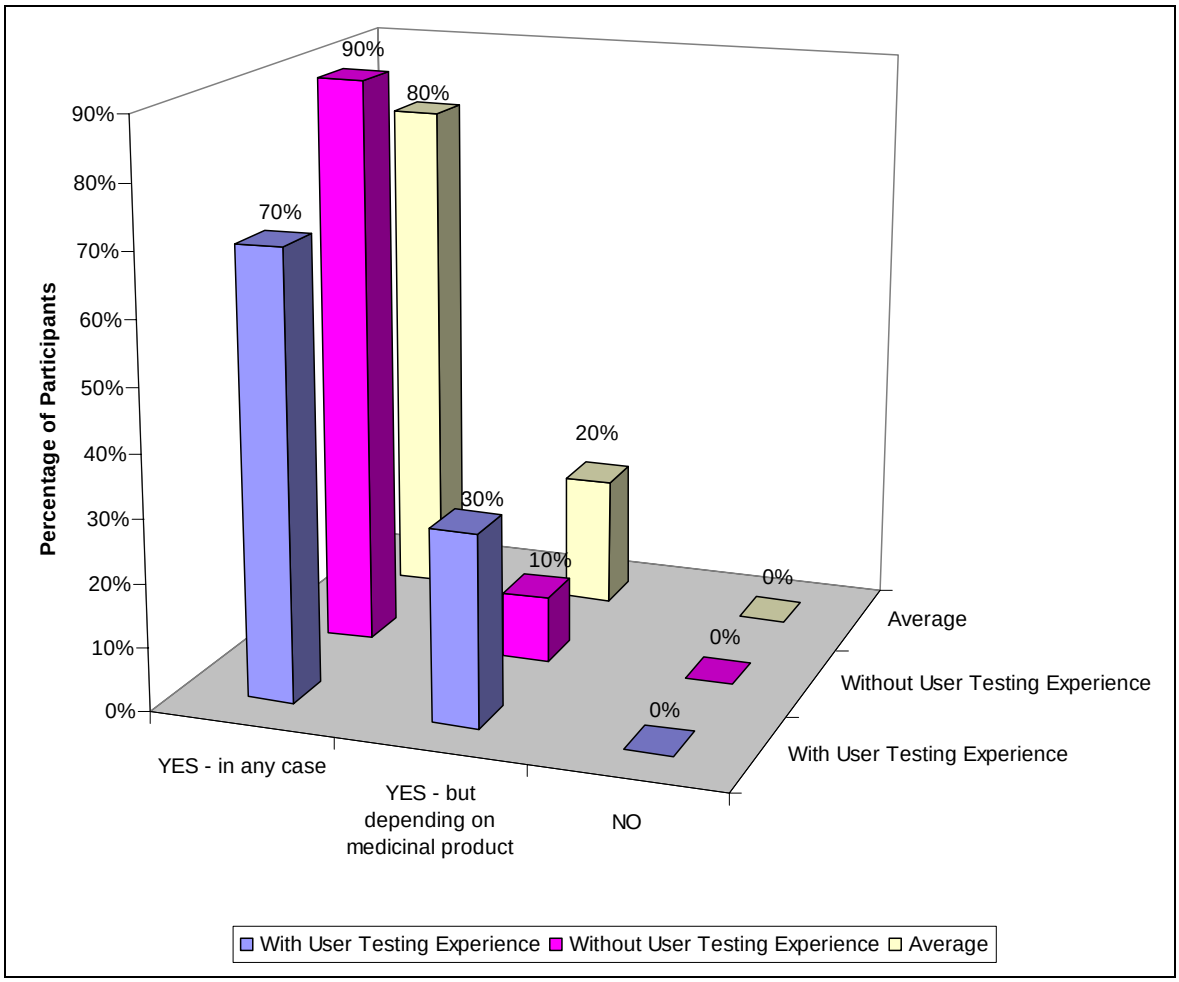

Figure 11: Pregnancy and Lactation - Considered as Key (Safety) Information

4.3.3.6 Dosage

The majority (87% in the average) classified dosage as key (safety) message in user testings. The percentage of experienced and un-experienced colleagues was similar (83% and 90%, respectively) - see Figure 12.

Several comments were raised:

- In case of potential safety or indication issues
- If the patient administers the drug by himself: yes; if it is administered by the physician: no
- Not relevant for patients, if product applied/stored by doctors/nurses/etc. only (e.g. vaccines)

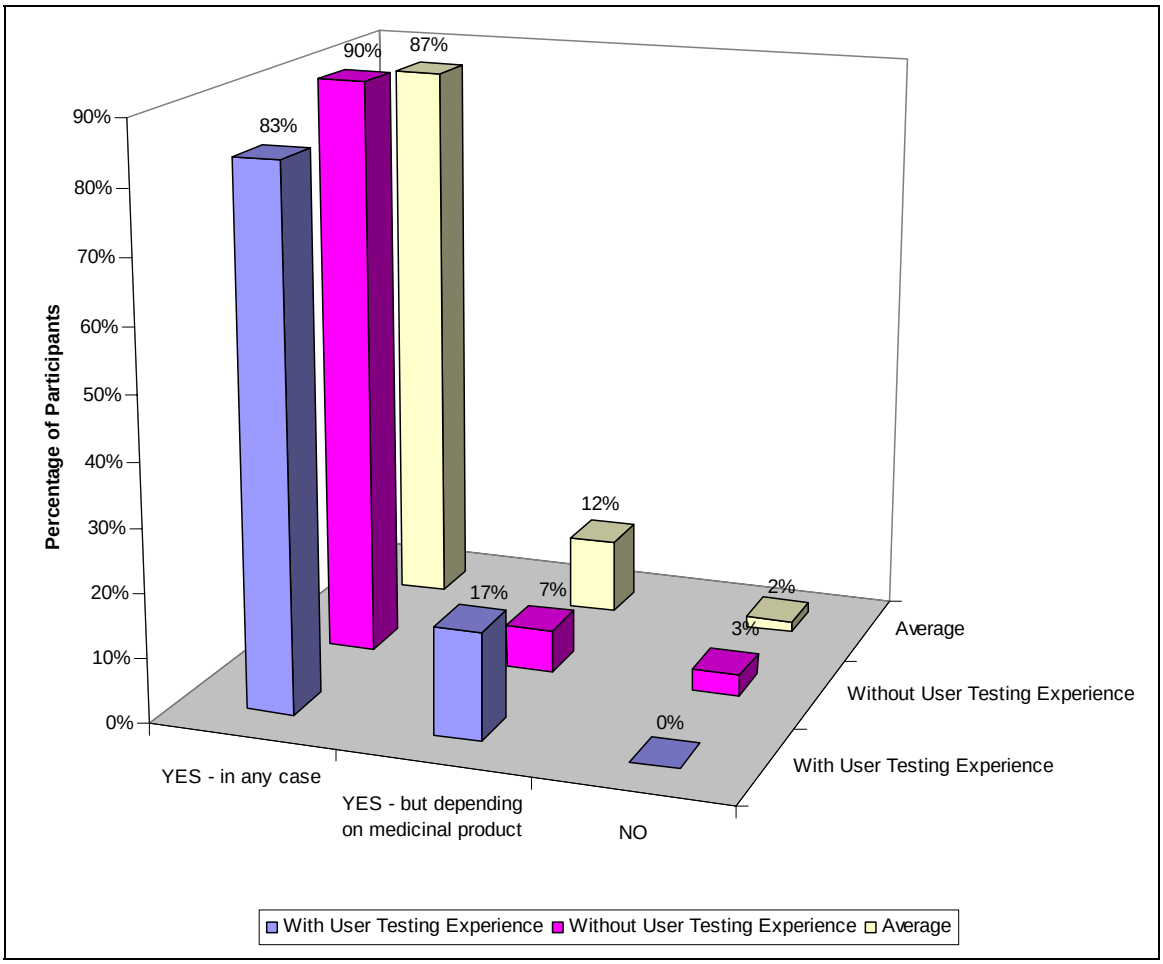

Figure 12: Dosage - Considered as Key (Safety) Information

4.3.3.7 Application

The participants with user testing experience had a heterogeneous view on the application of a medicine as key (safety) information: 43% stating “YES - but depending on the medicinal product”, 40% “YES - in any case” and 17% “no”. In contrary, 79% of the un-experienced colleagues classified application as key (safety) message in any case. This was reflected in the average classification of all participants (59%) – see Figure 13.

Additionally, several comments were provided:

- As soon as something is different from patient expectation
- If the patient administers the drug by himself: yes; if it is administered by the physician: no
- Not relevant for patients, if product applied/stored by doctors/nurses/etc. only (e.g. vaccines)
- Might be of high importance depending on the risk related to application (e.g. cytostatics administered into an artery)

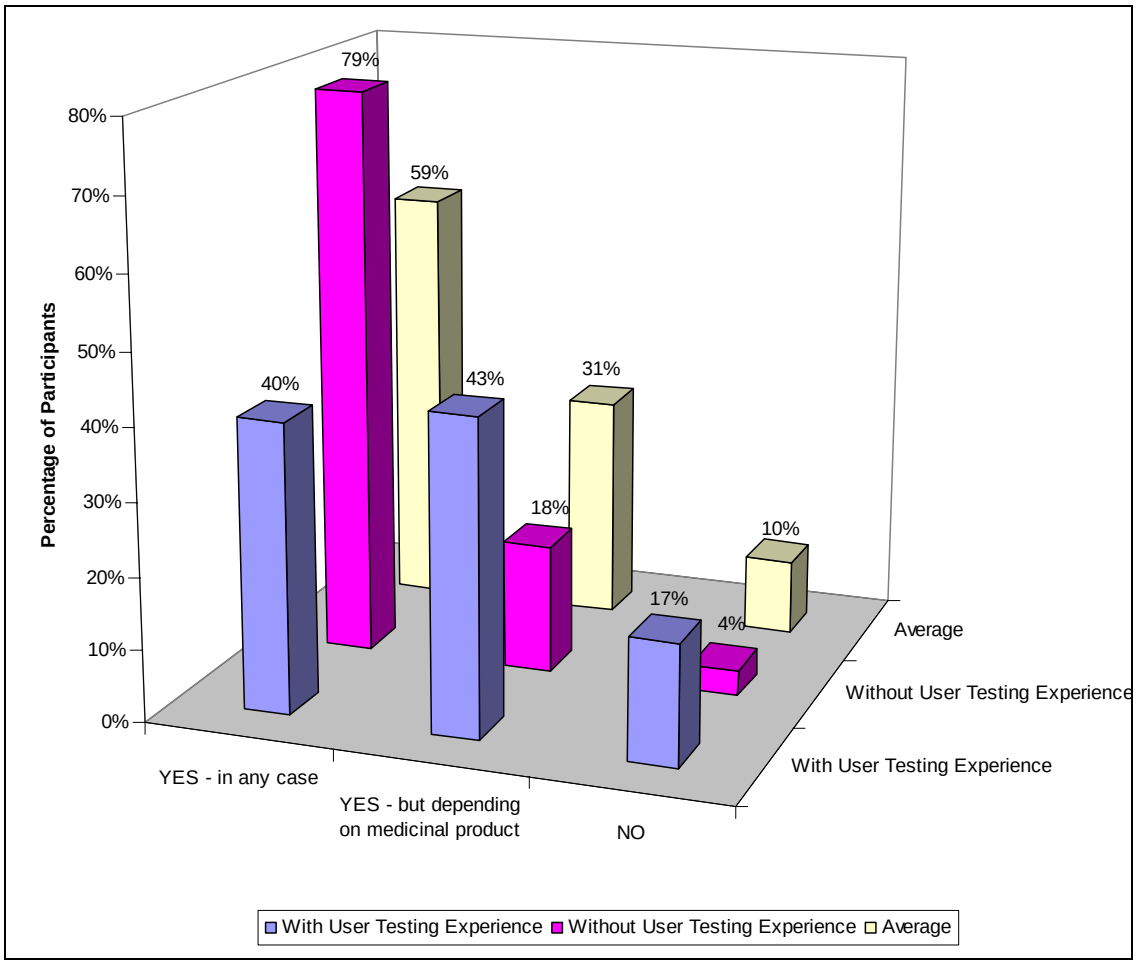

Figure 13: Application - Considered as Key (Safety) Information

4.3.3.8 Special Patient Group(s)

Information on special patient group(s) as key (safety) information in user testings was classified very similarly by experienced and un-experienced colleagues with 47% versus 45% “in any case” and 53% versus 52% “depending on the product” resulting in an average of 46% and 53% . However, there was no clear consensus on that topic – see Figure 14.

Additionally, some comments were provided:

- As soon as something is different from patient’ expectation
- If the patient administers the drug by himself: yes; if it is administered by the physician: no
- Not relevant for patients, if applied/stored by doctors/nurses/etc. only (e.g. vaccines)
- Might be of high importance depending on the risk related to application (e.g. cytostatics administered into an artery)

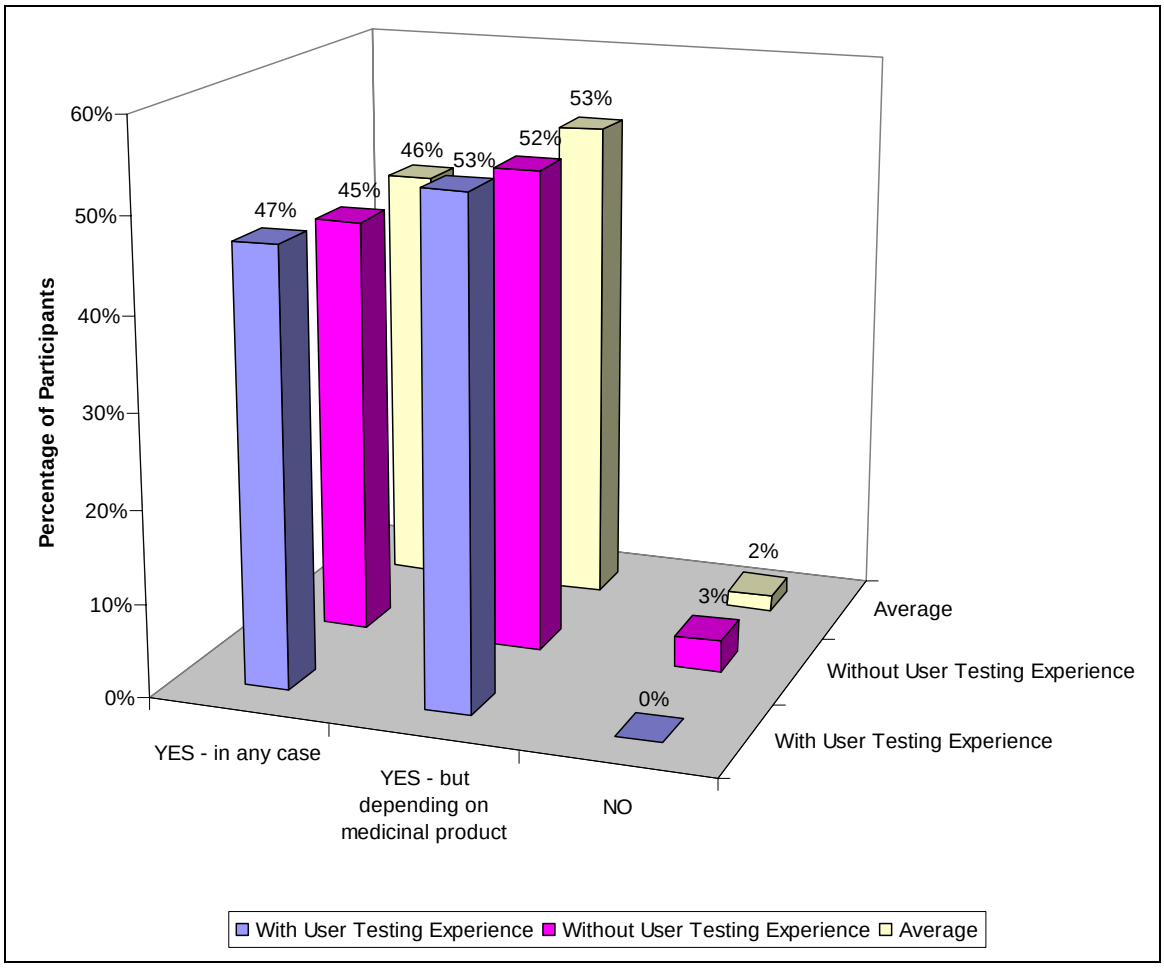

Figure 14: Special Patient Group(s) - Considered as Key (Safety) Information

4.3.3.9 Duration of Usage/Intake

The assessment on duration of usage/intake as key (safety) information in readability testings was comparable to the assessment of application (see section 4.3.3.7 Application): With a clear decision by the participants without experience in user testings in favour of “YES – in any case” (82%), but with an uncertain categorisation by the experienced: 50% - “YES – in any case” and 47% - “YES – but depending on medicinal product”. This leads to a majority of 2/3 (66%) for duration of usage/intake as key (safety) information in average – see Figure 15.

The following remarks were given:

- Is normally decided by the physician (might be necessary for OTC products)
- In case of special concerns
- Only if the use is strictly limited to a certain timeframe (e.g. 1 week)
- Might be important, e.g. if the medicine is not to be used on a long-term basis or will lead to an addiction (e.g. laxative)

- Product available without prescription [Remark: This comment was in relation to "YES – but depending on medicinal product"]

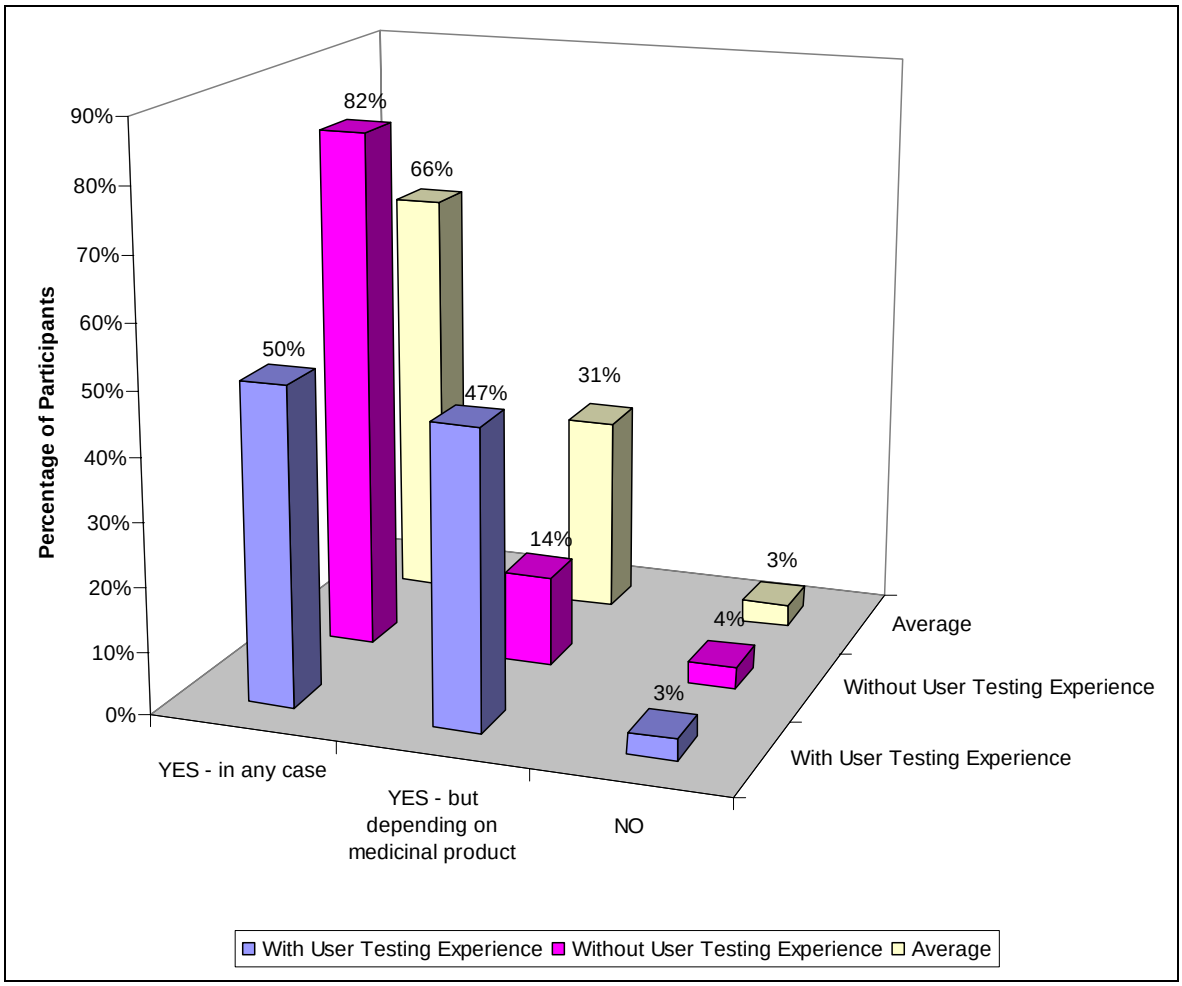

Figure 15: Duration of Usage/Intake - Considered as Key (Safety) Information

4.3.3.10 Overdosing

For the information on overdosing as key (safety) information in readability testings there is an obvious categorisation as "YES – in any case" by un-experienced participants (75%) but an unclear one by the experienced attendees: In any case (55%) and dependent from the medicinal product (42%). This results in an overall majority of overdosing as key (safety) message in user testings (64%) – see Figure 16.

The following was remarked:

- Only if there is an action for the patient (either call doctor or go to hospital etc…)
- Only if overdosing causes severe side effects
- Important if overdosing is risky for the patient

- Depending on the effect

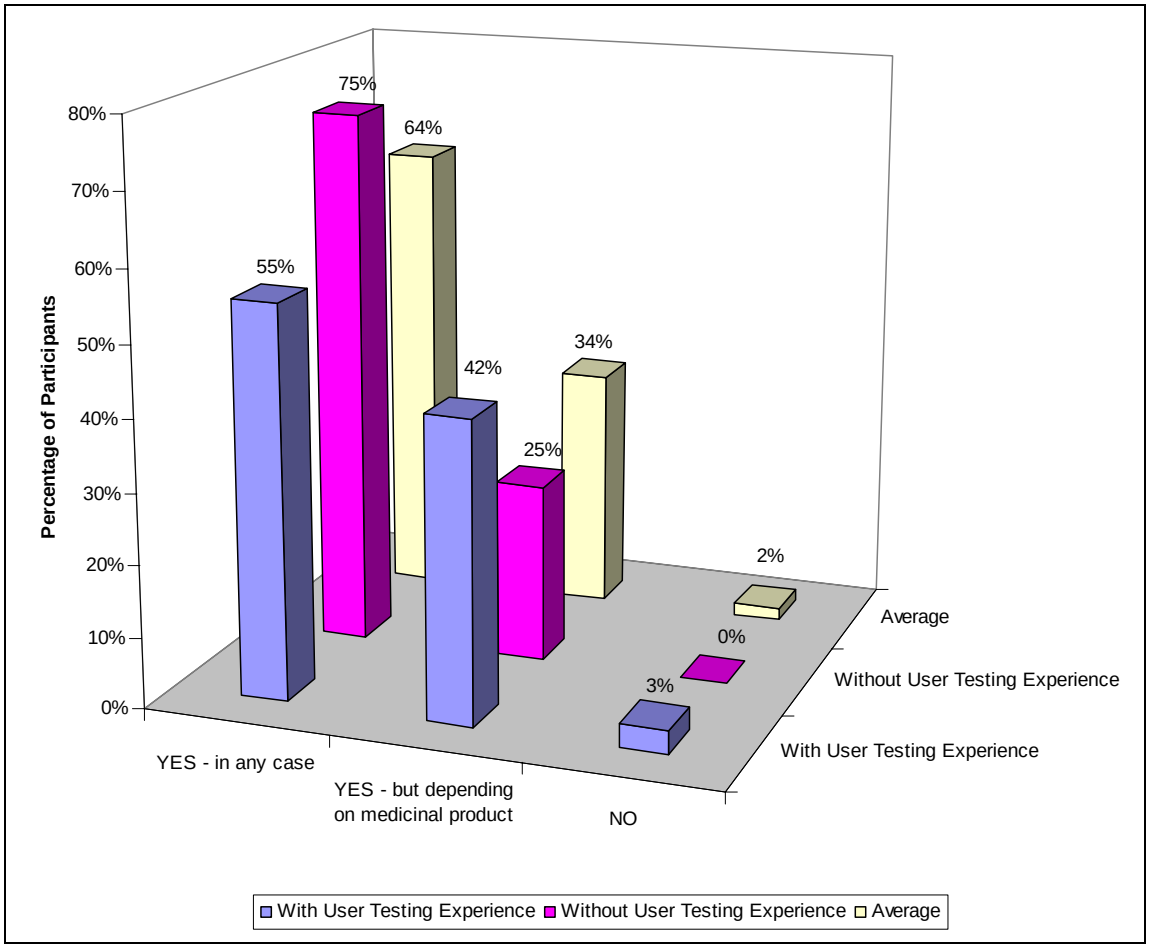

Figure 16: Overdosing - Considered as Key (Safety) Information

4.3.3.11 Omission to Use/Take Medicine

Similarly to the previous section, the information whether the intake/usage of a medicine has been omitted was classified as core (safety) information in any case by 64% of participants without user testing experience; there was no clear decision by the experienced ones: 47% in any case and 50% depending on the product. This finally led to a mean of 55% in the category "YES – in any case" – see Figure 17.

The notes were as follows:

- Yes, if there is some specific action necessary
- In case of serious effect
- Especially of interest for hormonal products
- In case of special concerns
- Depends on importance of treatment (e.g. omission of HIV treatment → causes resistance of HI virus, discontinuation of antipsychotic treatment might cause relapse)

- Depending on the risk
- Not clear what is meant

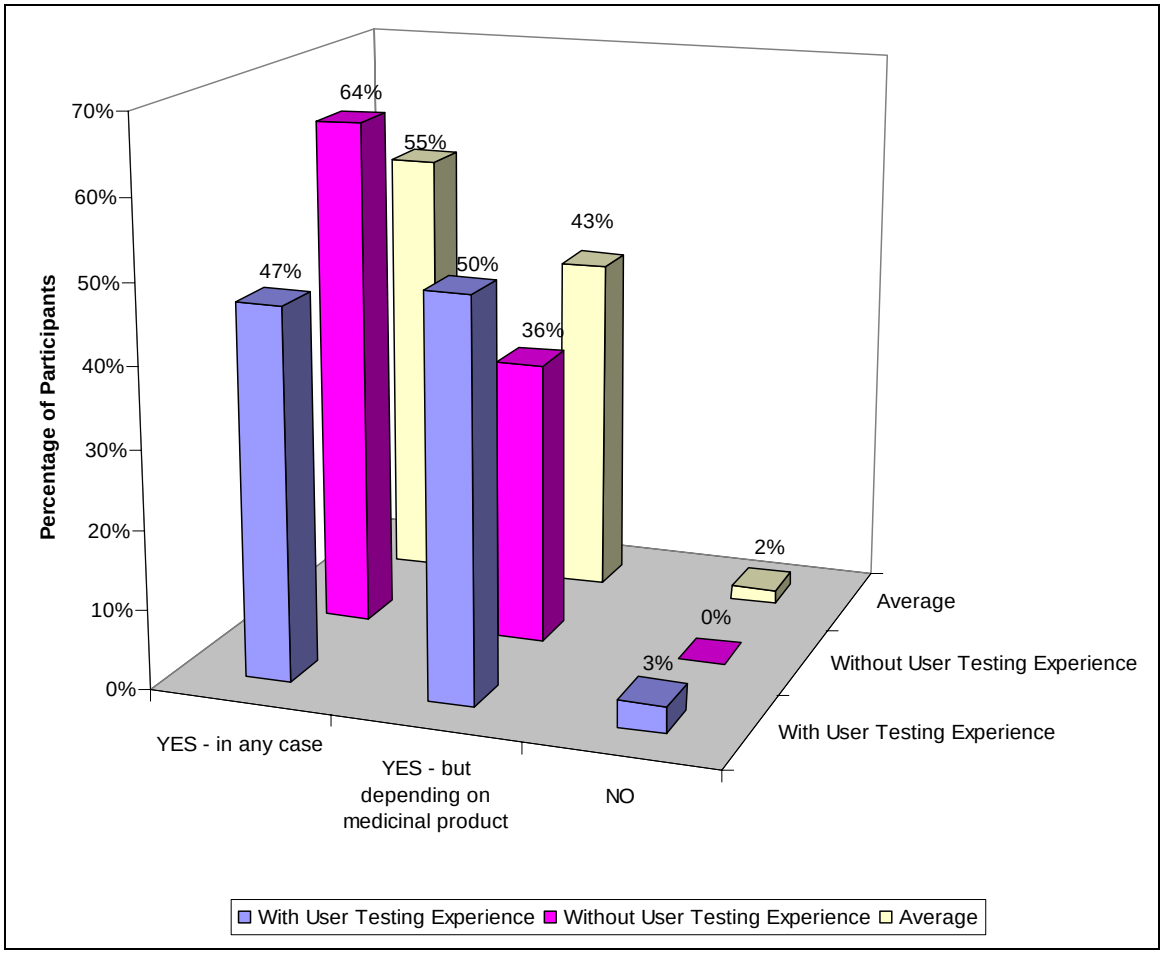

Figure 17: Omission to Take/Use Medicine - Considered as Key (Safety) Information

4.3.3.12 Stop Using/Taking Medicinal Product

The package leaflet section “stop using/taking medicinal product” was categorised as key (safety) message of the leaflet in any case by the majority of subjects without experience in readability testings (75%) but with bivalent opinion of experienced participants: 47% rated core (safety) information under any circumstance and 53% related to the medicinal product. In total, 60% consider stop using/taking medicine as key (safety) message for readability testings – see Figure 18.

Some additional comments were retrieved:

- Yes, if there is some specific action necessary e.g. consultation of physician, or rebound/withdrawal phenomenon
- In case of serious effect
- If certain circumstances have to be considered
- Only if the immediate stop of using the drug is associated with a risk for the patient

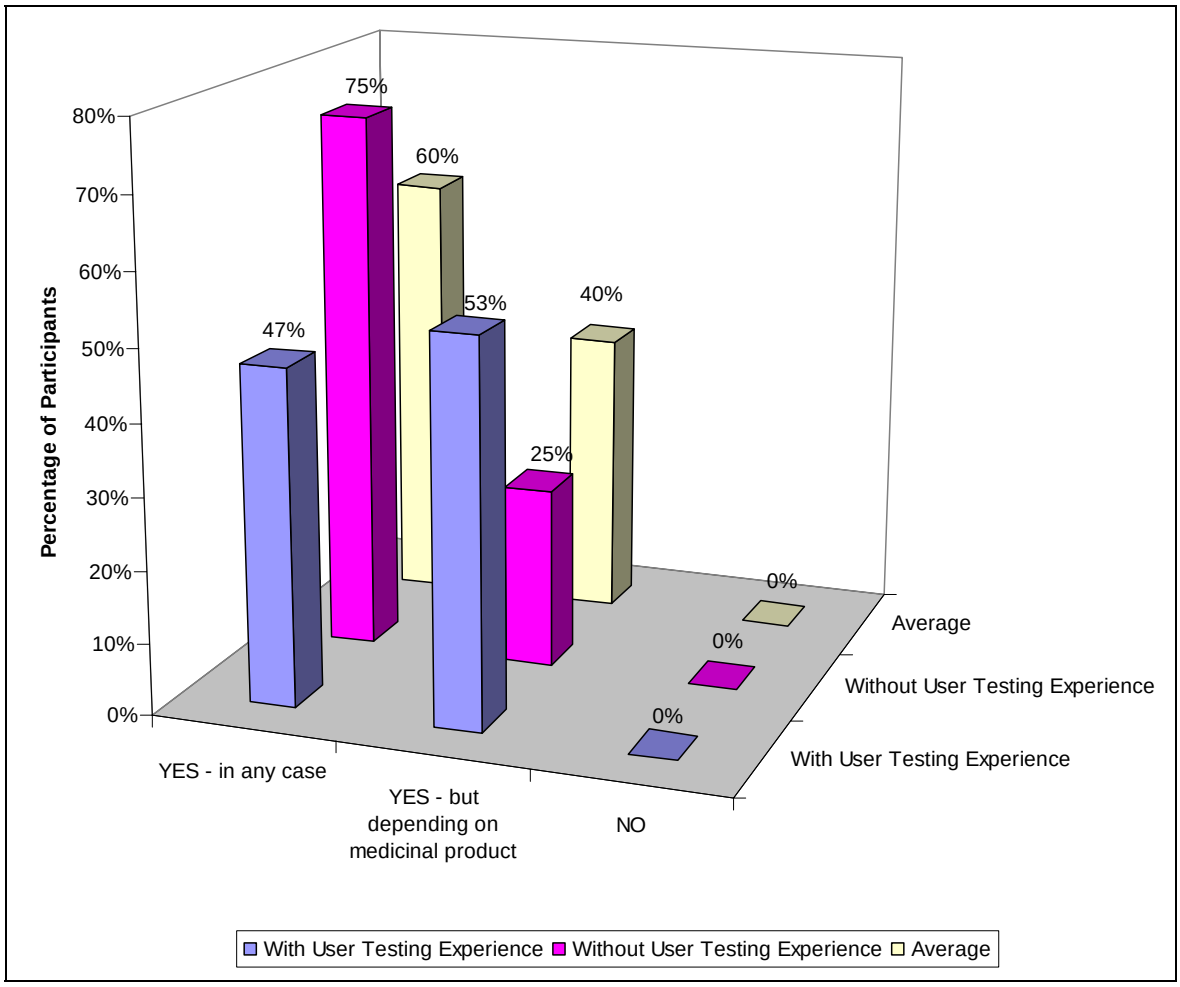

Figure 18: Stop Using/Taking Medicinal Product - Considered as Key (Safety) Information

4.3.3.13 Side Effect(s)

Overall harmony was expressed in the question whether side effect(s) were classified as core (safety) messages for user testings, with the majority of 97% by experienced colleagues and 93% by the un-experienced, resulting into an average of 95% - see Figure 19.

Furthermore, the subjects remarked the following:

- Particularly if the patient has to act in a specific way depending on the AR.
- Only severe or frequent side effects
- Vital, serious or long term side effects should be highlighted to draw the attention of patients

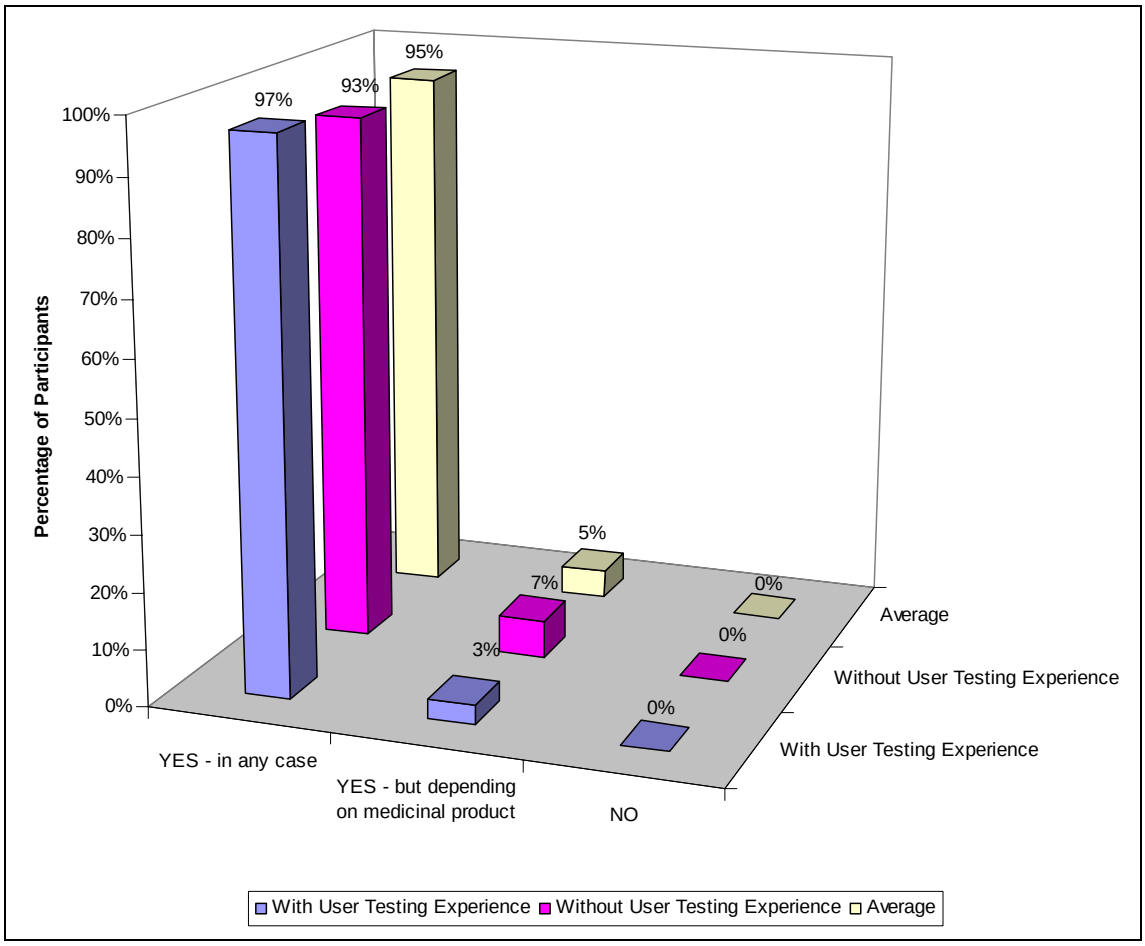

Figure 19: Side Effect(s) - Considered as Key (Safety) Information

4.3.3.14 Storage Conditions

On section 6 of the PL "storage conditions", the categorisation as key (safety) information in readability testings differed between the two parties: 55% of un-experienced subjects considered this information as core (safety) message in any way and 34% depending on the medicinal product. In contrary, 57% of the experienced colleagues classified it related to the product but only 43% as key (safety) information in any case. This resulted in an average of 49% judging the information how to store medicines as key (safety) information for user testings in any case and, at a similar percentage level (46%) depending on the product (Figure 20).

Some items supporting the considerations were provided, too:

- If different from room temperature
- If the patient administers the drug by himself: yes; if it is administered by the physician: no
- Only if special conditions are required (not room temperature but e.g. 2-8°C)
- Necessary, if incorrect storage could cause a significant change in quality prior to formal expiry date stated

- Might be of higher importance depending on medicinal product, i.e. insulin or vaccines

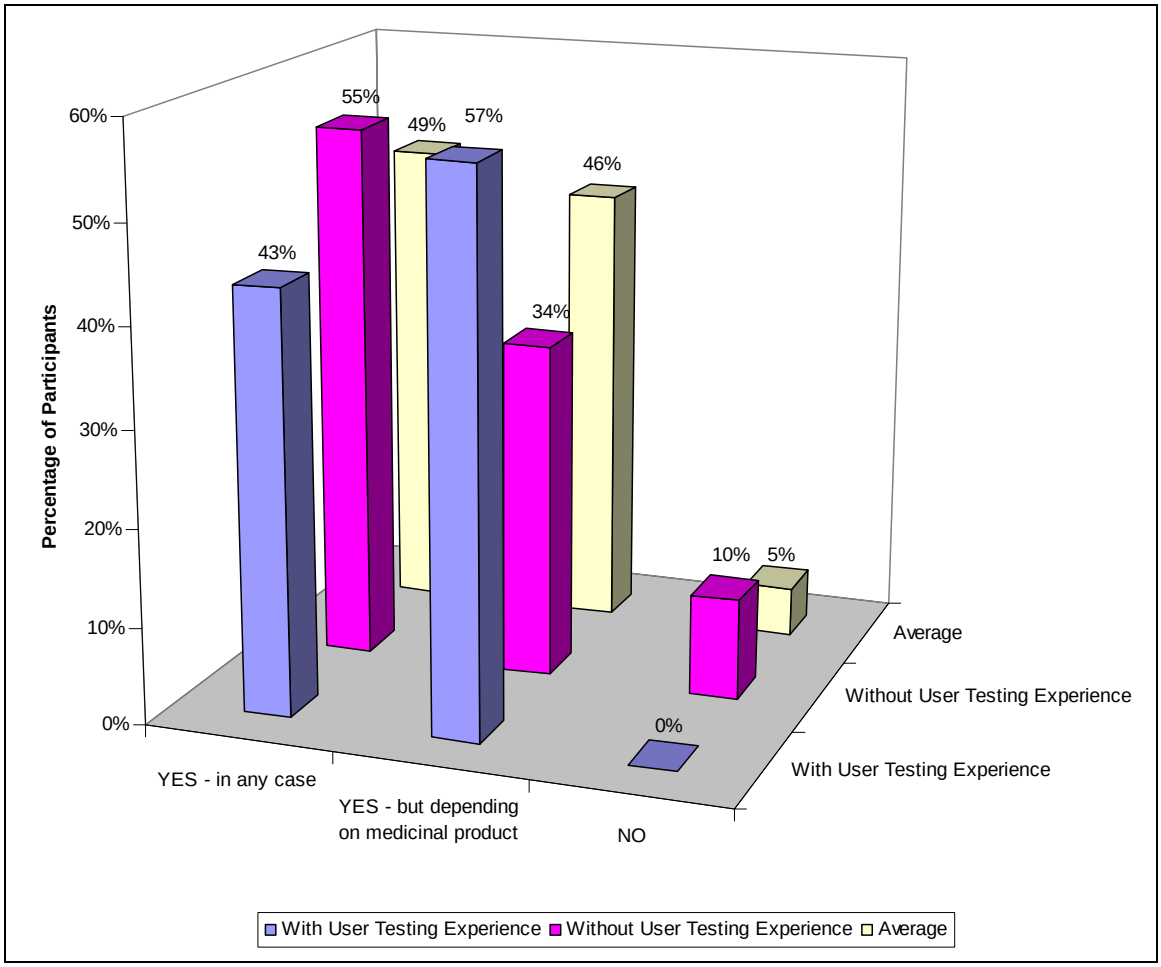

Figure 20: Storage Conditions - Considered as Key (Safety) Information

4.3.3.15 Expiry

For the judgement whether the expiry information on medicinal products is to be classified as key (safety) message in user testings a wide difference was retrieved between the two parties:

44% of participants with readability testing know-how considered it as “YES – in any case” but also 41% as “NO”. Therefore, no preference could be assessed. On the other hand, subjects without experience categorised it with a slight majority of 57% as core (safety) information. The average outcome (51%) for expiry as key (safety) information was also not conclusive – refer to Figure 21.

A few comments were given:

- Only if there is a real hazard due to degradation products.
- Not relevant for patients, if applied/stored by doctors/nurses/etc. only (e.g. vaccines)
- Sufficient on inner/outer packaging

- Might be of higher importance depending on medicinal product, i.e. insulin or vaccines

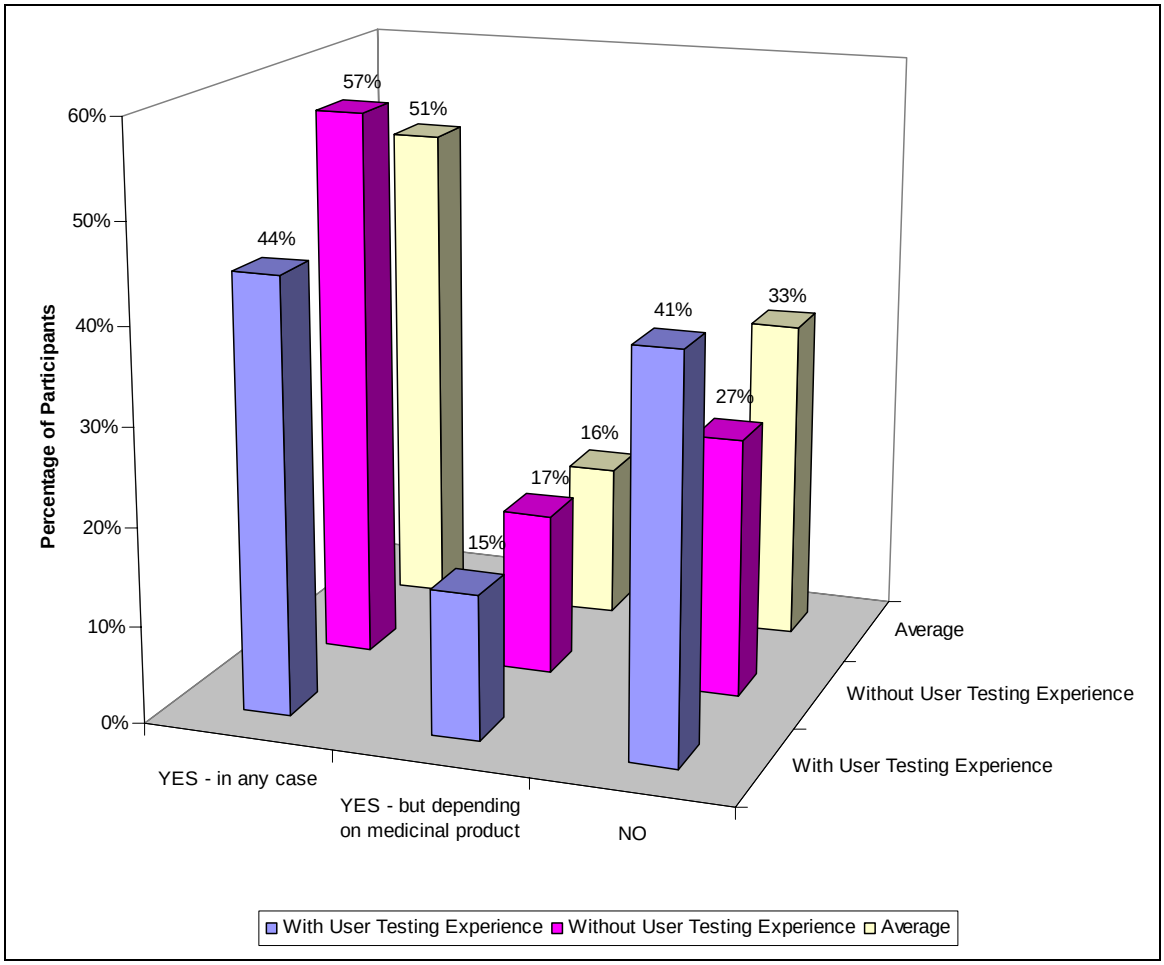

Figure 21: Expiry - Considered as Key (Safety) Information

4.3.3.16 Composition of Medicinal Product

According to Figure 22, no clear preference was given on the importance of the composition of the medicinal product as key (safety) message in user testings with 39% of the experienced participants classifying “YES – in any case” and 36% as “no”. For subjects without knowledge in those tests, the majority (50%) judged this information as relevant core (safety) message in any case, corresponding to an overall rating of 45%.

The following comments were given:

- Scientific knowledge/understanding of "average" patient in doubt
- If there is a safety issue (e.g. lactose intolerance, this is addressed in a different section (e.g. warnings)
- Only in case of intolerance or interaction

- API always, excipients e.g. if potential allergens are included
- Excipient warnings may be key information though
- In case of hypersensibility [Remark: This comment was in relation to "YES – but depending on medicinal product"]

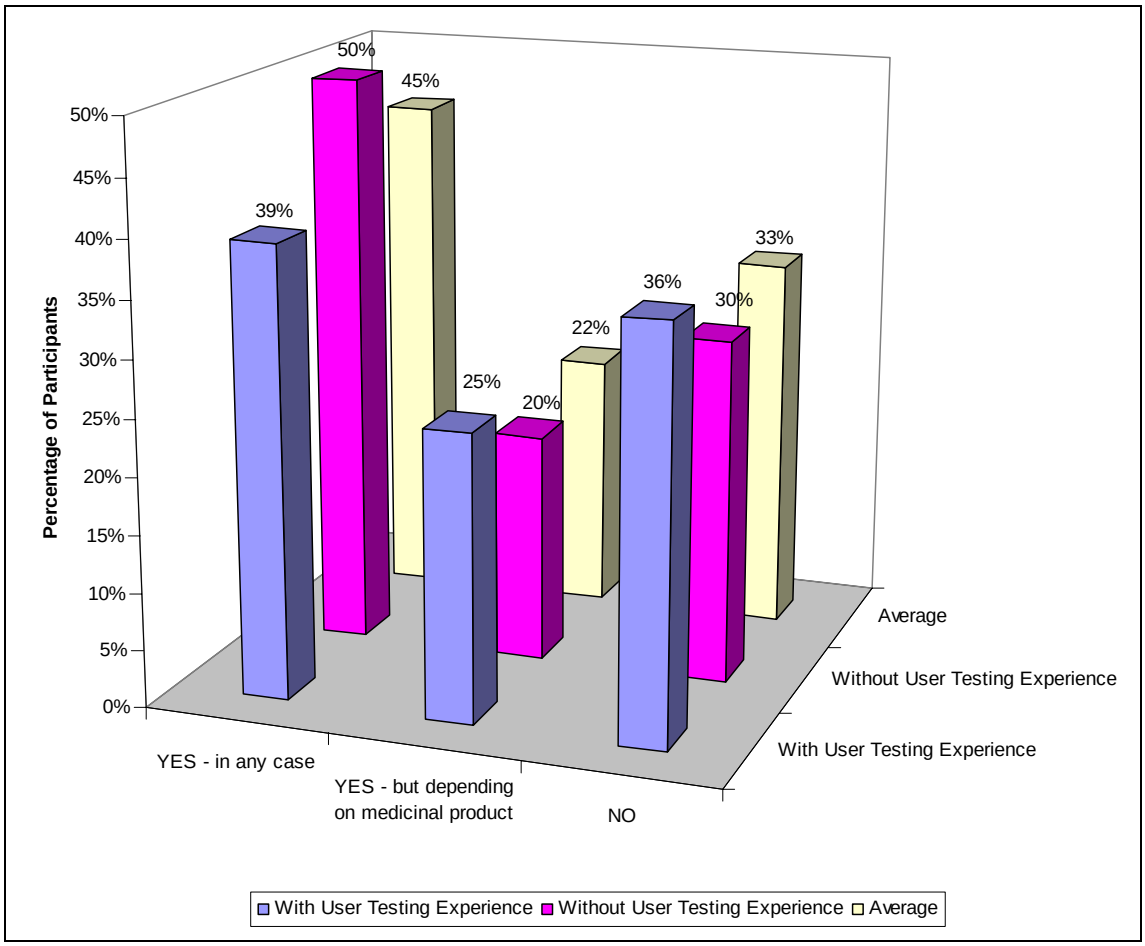

Figure 22: Composition of Medicinal Product - Considered as Key (Safety) Information

4.3.3.17 Appearance of Medicinal Product

During the classification of appearance as relevant key (safety) message in user testings, the most uncertain result of this survey was retrieved: Each option was voted by about 1/3 of the participants – no matter if with or without user testing experience. Only the un-experienced showed preference for "YES – depending on the medicinal product" (48%). This still led to a majority of 40% in average for this category but without this percentage being representative – see Figure 23.

This uncertainty might also be represented by the highest number of comments on this:

- E.g. if different appearances are related to different dosages

- Only if altered appearance indicating damaged product is likely, or if appearance is 'strange'.
- Especially important for detecting counterfeit medicines
- If there are special concerns, e.g. cloudiness in solution for injection as sign of deterioration
- Might be important, e.g. solution for injection which is not clear, or might also not be important (colour of capsules)
- Some products are expressive or highly desired and it could be interesting in case of false copies sold on internet and things like that

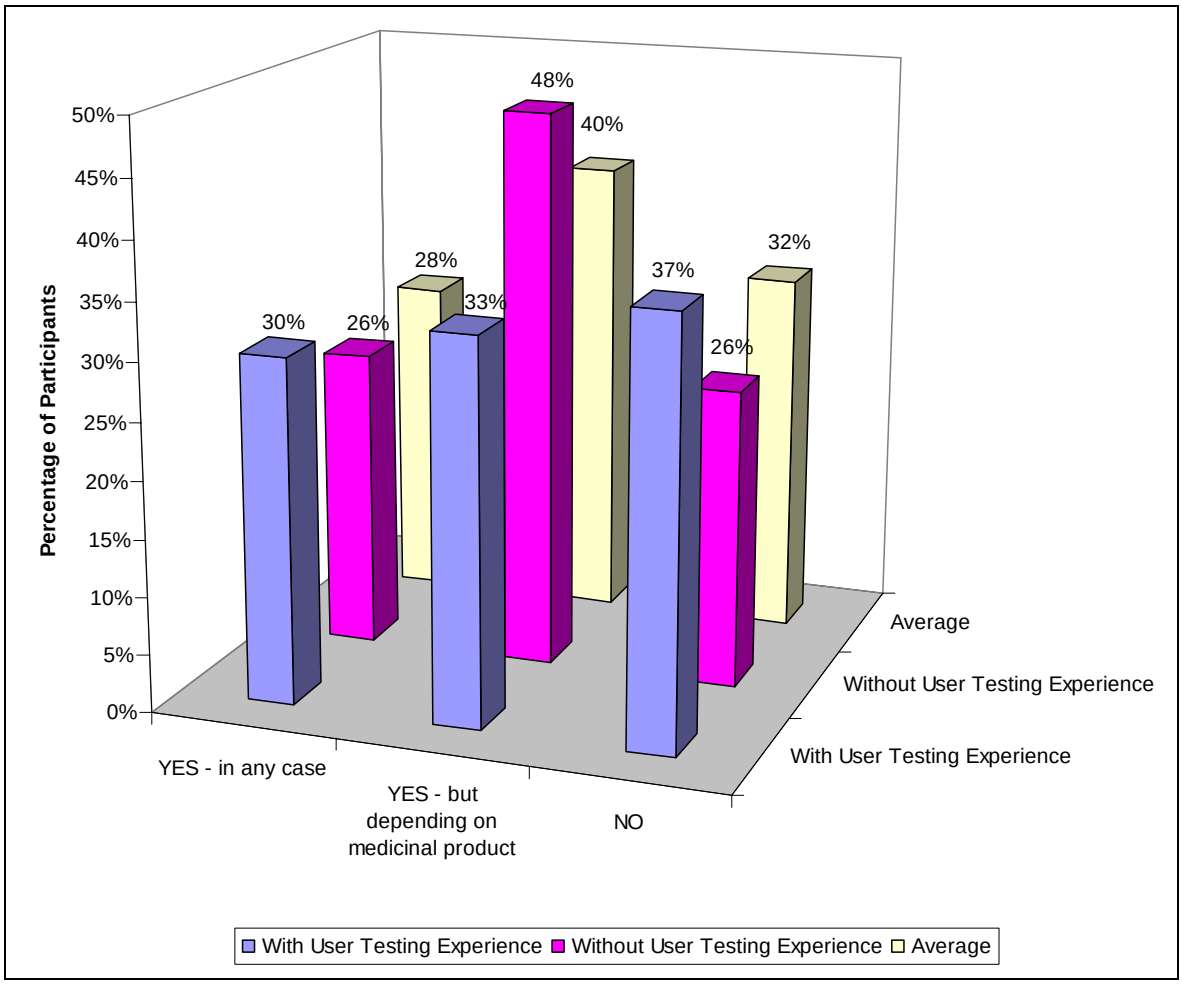

Figure 23: Appearance - Considered as Key (Safety) Information

4.3.3.18 Pack Size(s)

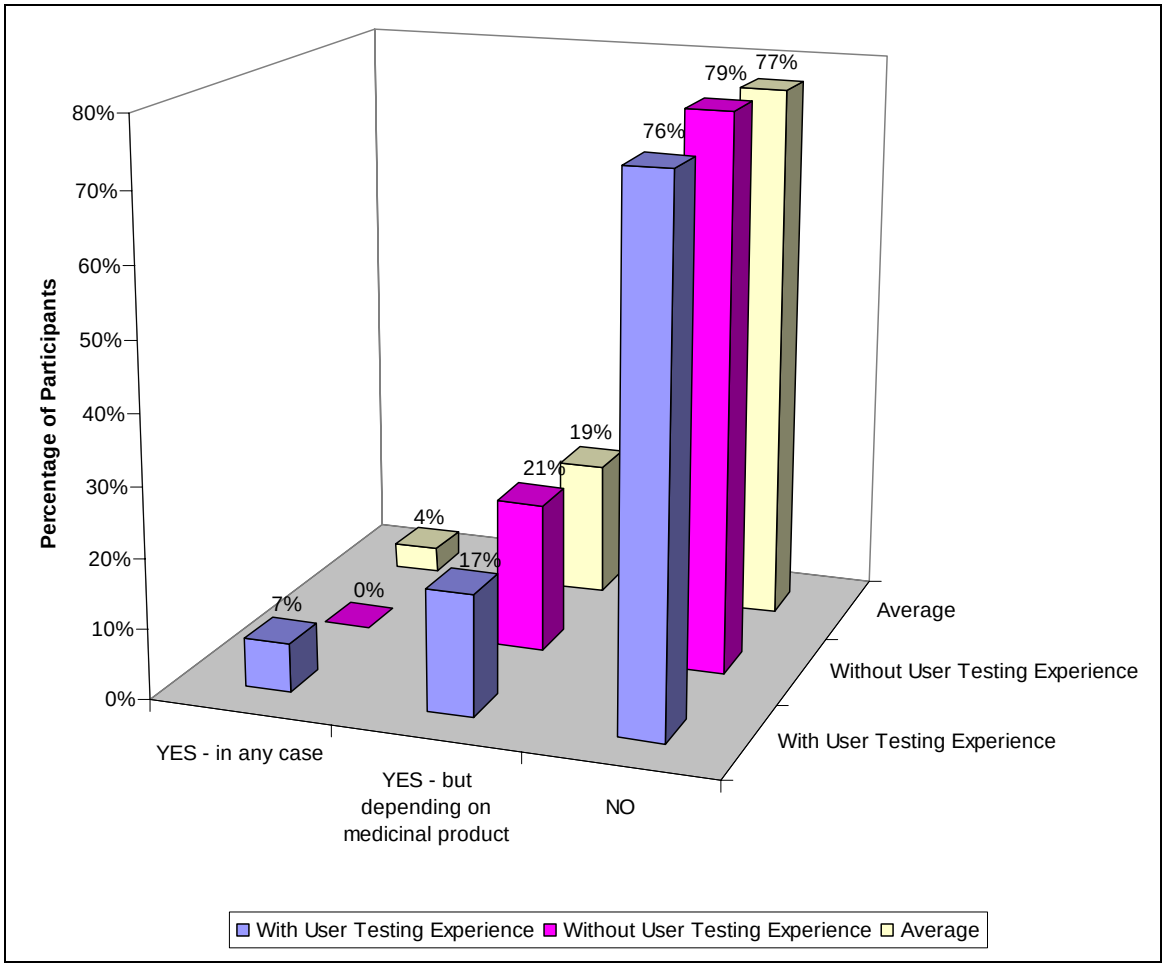

Figure 24: Pack Size(s) - Considered as Key (Safety) Information

Most of the participants of this survey had one opinion on the information on the pack sizes available for one medicinal product not to be relevant key (safety) message in user testing with a mean of 77%. This result derives from the unity of both parties on this question (76% and 79%) - see Figure 24.

The one and only note provided was:

- Only if there is a potential situation (loosing a tablet) which would make self-administration impossible, as there is no replacement etc …

4.3.3.19 Marketing Authorisation Holder

Pretty obvious was the categorisation of the name and address of the marketing authorisation holder as no key (safety) information for the conduction of user tests with a mean of 79%. This reflects the same tenor in experienced subjects (83%) and un-experienced ones (75%) as presented in Figure 25.

Only one (1) remark was to be retrieved:

- Patients are more focussed on products than on MAH

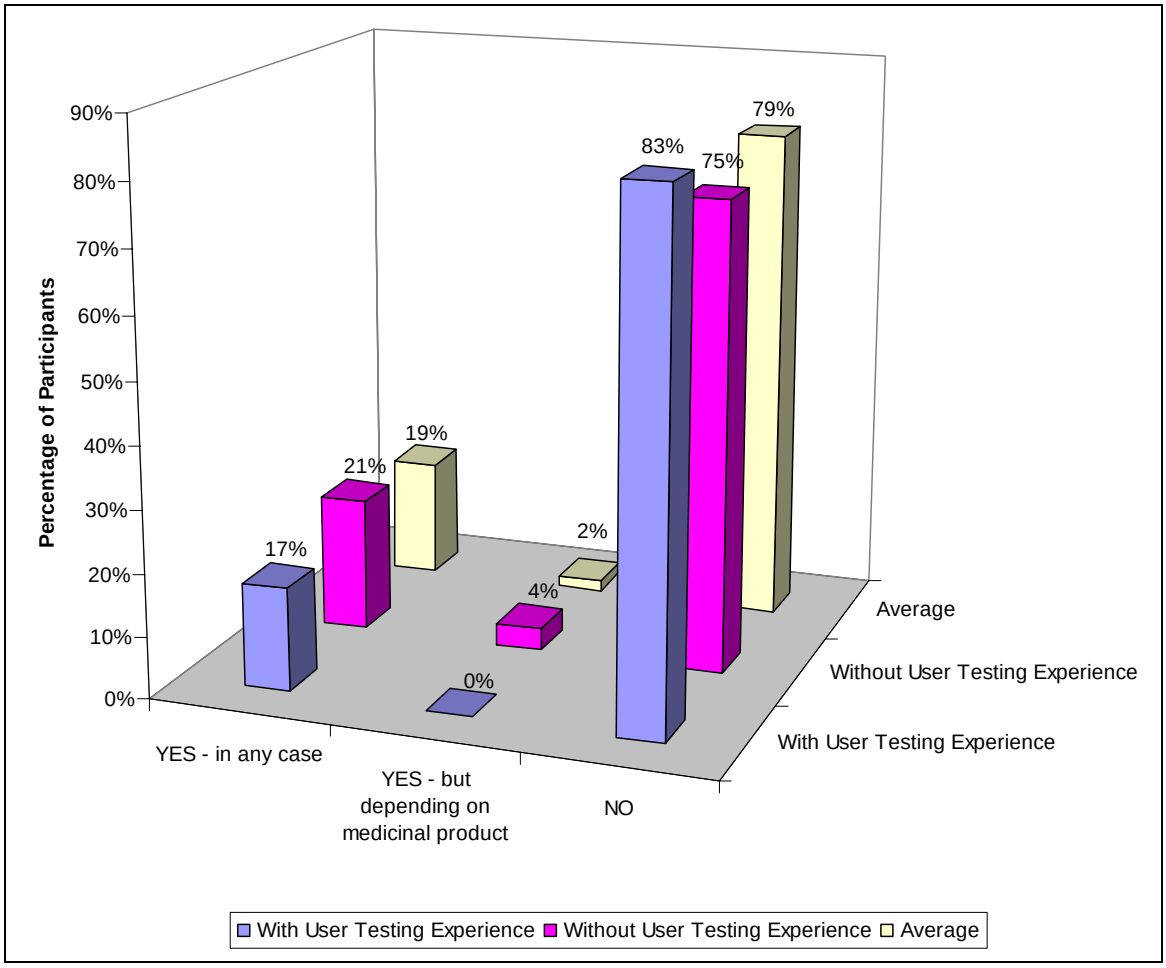

Figure 25: Marketing Authorisation Holder - Considered as Key (Safety) Information

4.3.3.20 Manufacturer(s)

As shown in Figure 26, an overwhelming judgement for “manufacturer(s)” as irrelevant information for readability testings was provided by experienced (96%) and un-experienced (86%) participants. In conclusion, the mean of 91% voted for the information regarding the manufacturer(s) as not to be considered in user testings.

The remarks were:

- Not relevant to patient
- This information normally is not of interest for the consumer, but for CAs.
- Relevant, e.g. biologicals

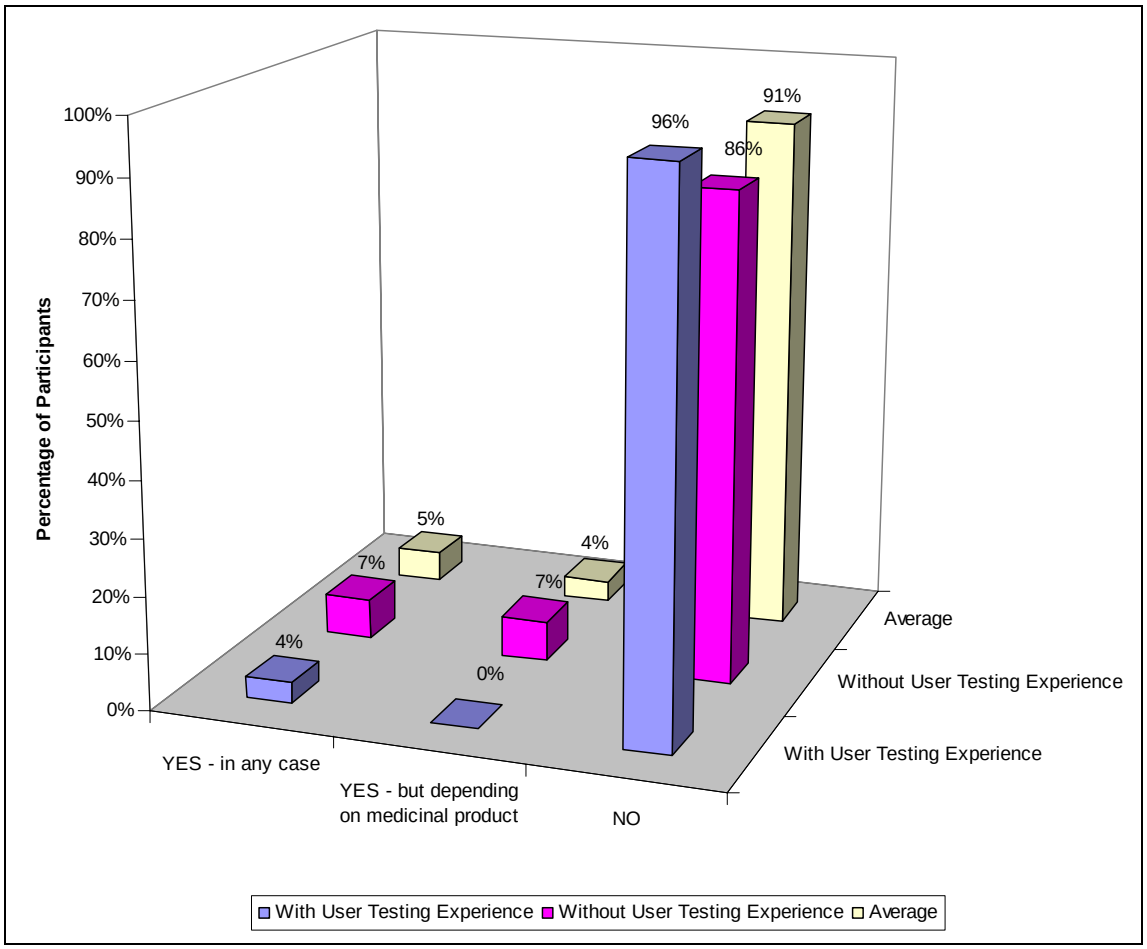

Figure 26: Manufacturer(s) - Considered as Key (Safety) Information

4.3.3.21 Date of Revision/Date of Approval

A clear categorisation for “date of revision/application” as not relevant core (safety) information in user testings was provided by participants either with testing experience (90%) or without (80%) and led to an average of 85% (see Figure 27).

- For the user, this is not important. Revision dates only important within SmPC for the physician
- Not relevant to patient as long as available information are reflecting current status

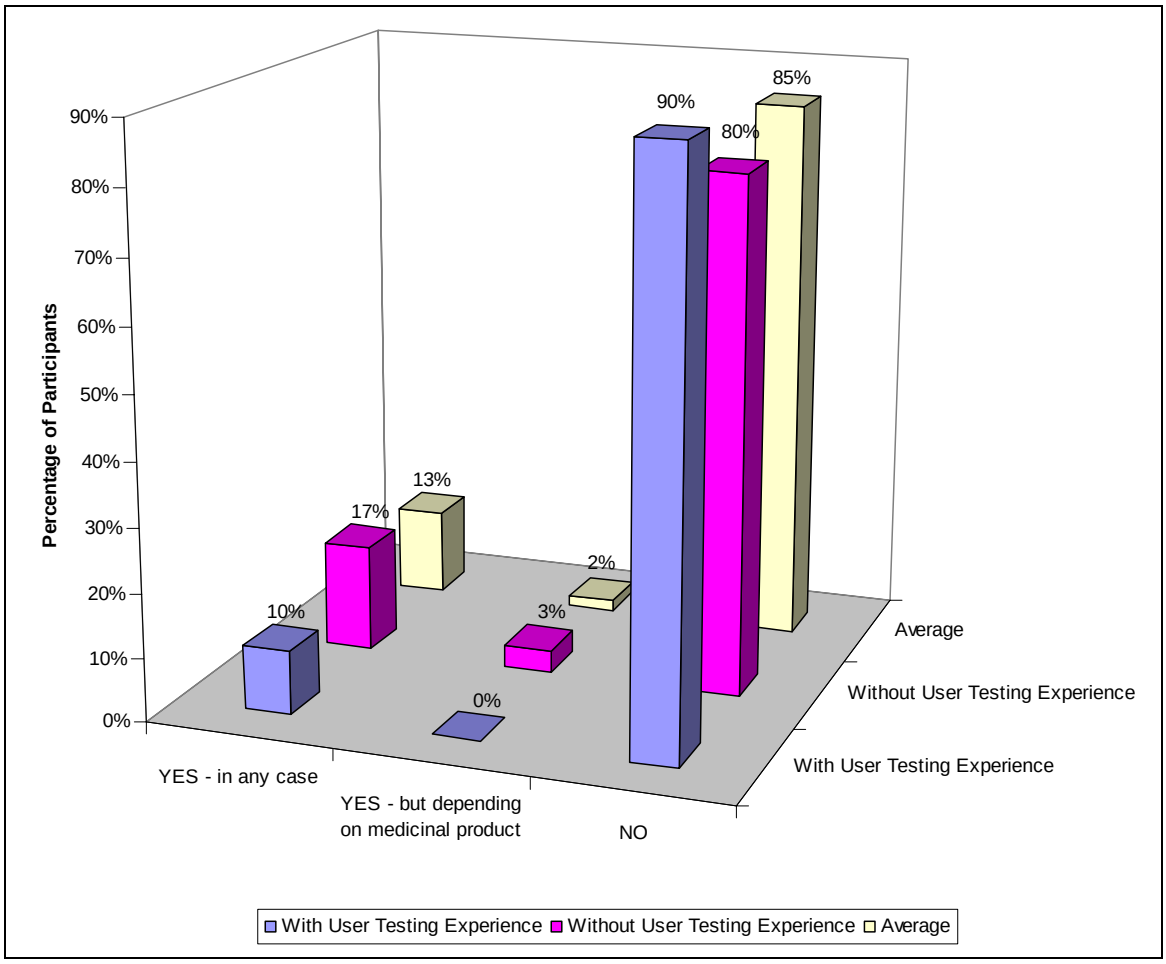

Figure 27: Date of Revision/Date of Application - Considered as Key (Safety) Information

4.3.3.22 Legal Status

The majority of participants did not classify the legal status as key (safety) message for readability user testings. This applied for both parties experienced as well as un-experienced at a comparable percentage (67% versus 71%) and resulting in a mean of 69% (see Figure 28).

The subjects commented as follows:

- Not relevant to patient the moment a product is commercially available
- Only if limited to prescription [Remark: This comment was in relation to “YES – but depending on medicinal product”]
- Different approaches for OTC even within the EU

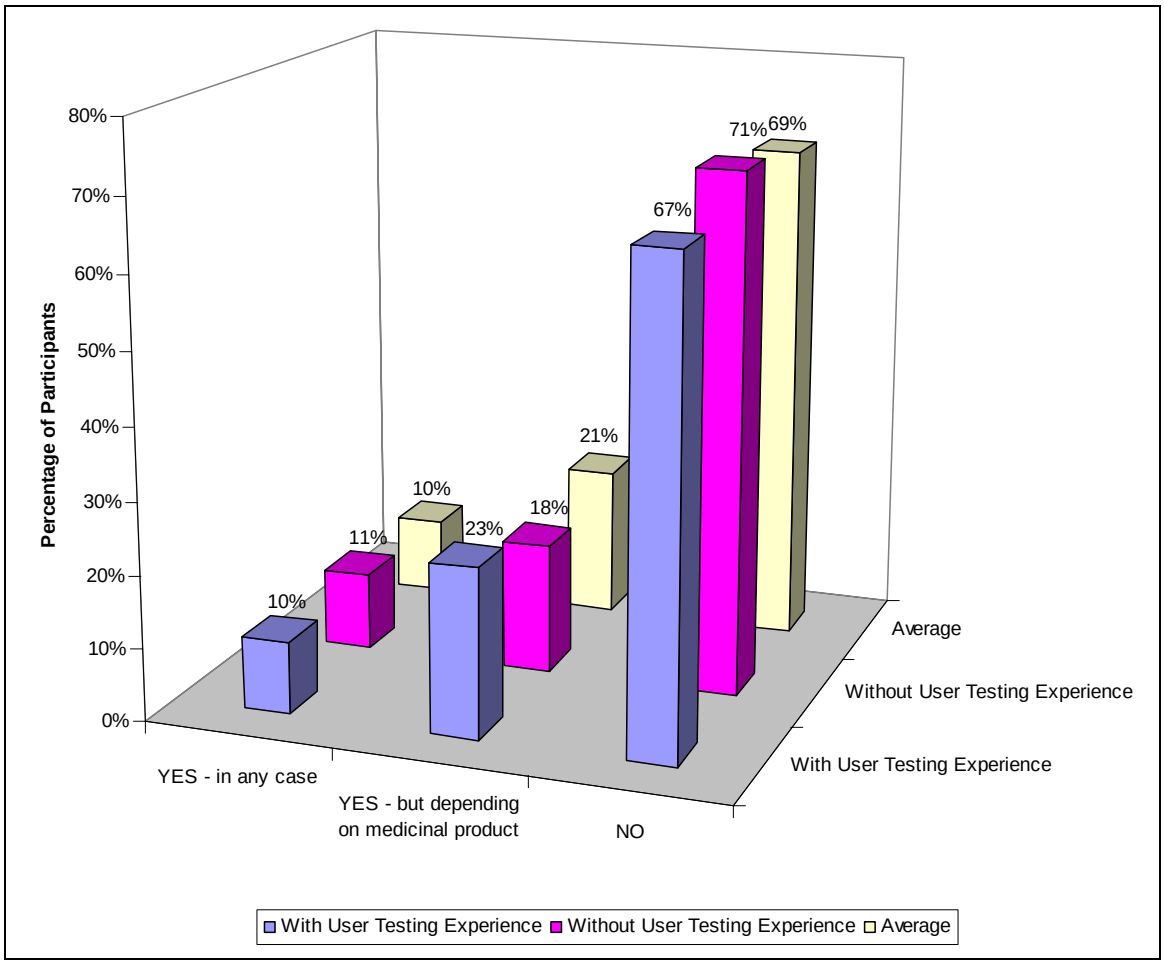

Figure 28: Legal Status - Considered as Key (Safety) Information

4.3.4 Parties to Be Involved into Definition

In Question 10, participants were asked what parties they would involve/have involved to define key (safety) information of a medicinal product. Multiple responses were possible.

The majority (33%) named Regulatory Affairs, followed by Pharmacovigilance (28%) and Clinical (23%).

The fourth option “other party” was chosen by 14%. The attendees of the questionnaire were requested to specify this choice further, resulting in the following:

- CMC (Chemistry Manufacturing and Controls)
- Marketing
- Medical
- Medical Information
- Medical Sciences

- Common Sense
- User Testing Companies
- Physicians
- Pharmacokinetics
- Non-clinical Safety
- Patient Groups
- Case by Case Decision
- Development
- Language Service
- Production

In order to avoid masking the outcome of the option “Other Party”, the mentions were not summarised but every single different expression was presented. However, this might lead to misleading results for the option “Clinical”: Adding “Medical”, “Medical Sciences” and “Pharmacokinetics” to the party “Clinical” would lead to 43 (27%) and therefore to an equivalent percentage compared to “Pharmacovigilance” and “Regulatory Affairs” (each about 30%).

For detailed information please refer to Figure 29.

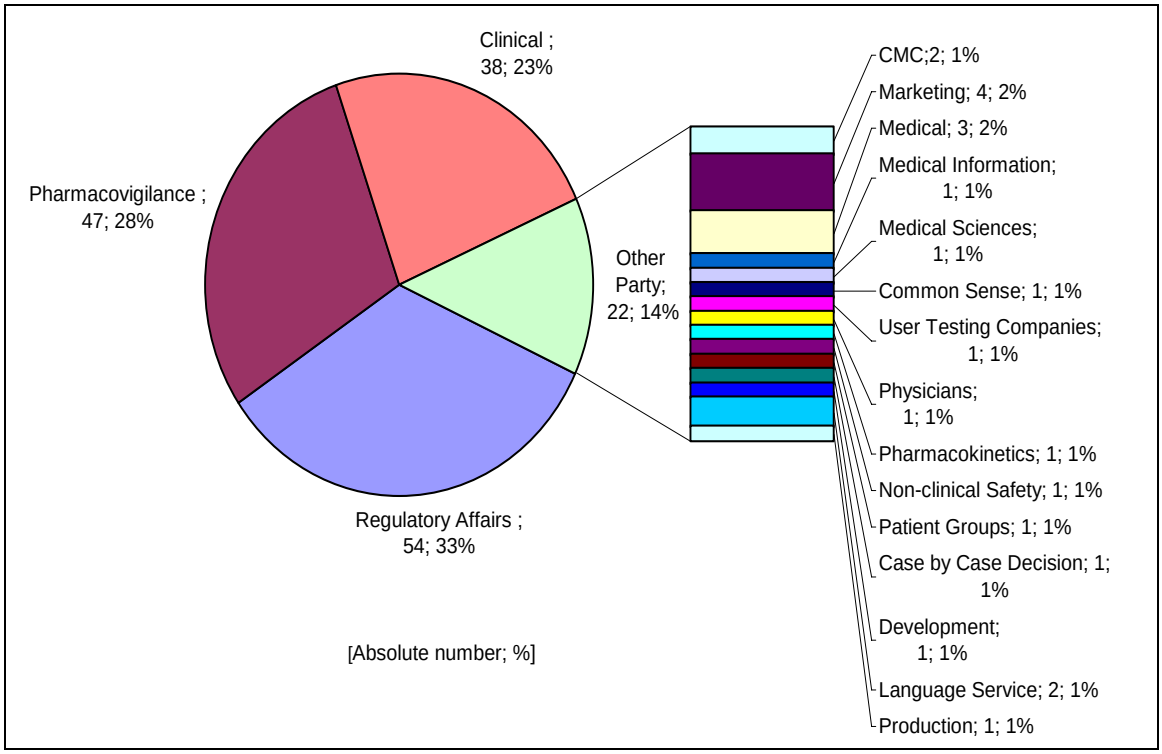

Figure 29: Parties to Be Involved into Definition

4.4 Current Discussions - Key (Safety) Information

4.4.1 General

The purpose of Question 11 and 12 was to assess the general relevance of key (safety) messages outside user testings with regard to current regulatory discussions.

In the same manner as explained in 4.3 Definition of Key (Safety) Information , non-experienced participants of the questionnaire were encouraged to also complete Questions 11 and 12 – see sections 4.4.2 and 4.4.3 below.

4.4.2 Awareness of EU Pharma Package

Following publication by the Commission (*COM (2007) 862*), proposals have been issued to amend the legislation to introduce harmonised rules on the provision of information on medicinal products subject to medical prescription to the general public.

As outlined in EC's *MEMO: Information to patients on prescription-only medicinal products (Dec 2008)*, the European Commission prepared a legal proposal on information to patients. Specifically, it proposes:

*"Those companies can make **information on** their **prescription-only medicines available** to the general public while **maintaining** the existing **advertisement ban.**"*

Within this topic, there are currently discussions what information should be made available, i.e. kind of key information for the patient information: *"Only **certain information** about prescription-only medicines may be published such as the patient leaflet or a **different presentation of its contents.**" (Citizen's Summary: Legal Proposals on Information to Patients by Pharmaceutical Companies, http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/patients/citizens_summary_info_to_patients_en.pdf, (Date of access: 01 Jun 2010))*

59% of the contributors were aware of the EU Pharma Package and its target to inform patients about key information of medicinal products.

No concrete action is planned by any company, yet. The reason given was that this is still under discussion at EU level and the outcome is not clear by today. However, it was also mentioned that the headquarters are aware and will take care of it. Some colleagues stated that they are not personally involved into these kinds of discussions due to their job activities.

4.4.3 Awareness of "SmPC Guideline" (Rev. Sept 2009)

The revised *"SmPC Guideline" (Rev. Sept 2009)* has also an impact on the adverse events section with new requirement to summarise the key (safety) information in section "4.8 Undesirable effects" / subsections "a. Summary of the safety profile" and "c. Description of selected adverse reactions". The guideline defines the content as follows:

a. Summary of the safety profile: "The summary of the safety profile should provide information about the most serious and/or most frequently occurring adverse reactions."

c. Description of selected adverse reactions: "This section should include information characterising specific adverse reaction which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice."

However, this requirement is exclusively concerned with side effects, which form only a small part of the key (safety) information. The "summary of the safety profile" and "description of selected adverse reactions" have to be defined for the SmPC in the same way as key (safety) information has to be defined for user testings.

The result of this questionnaire was that surprisingly a majority of 53% colleagues have no knowledge about this.

Nevertheless, half of those participants who were aware of the requirement (24%) stressed the fact that this is already state-of-the-art and current business practice since the draft guideline was published some time ago. One company stated that the SmPCs for most of their medicinal products have already been updated, accordingly.

4.5 Comments by Participants

All the colleagues (with and without user testing experience) had the chance to give overall comments on the questionnaire with very constructive content – see Table 5.

Comments by Participants
• I found sometimes the information on the same topic (e.g. a serious side effect) is spread in different locations (sections) because of the PIL structure
• After almost 5 years following implementation of the revised legislation, user testing still appears to be only a formal requirement. In my opinion, submissions are only checked for completeness in this regard. Following revisions of the SmPC / PIL, no update of the user testing was requested so far from an authority.
• Although the readability tests that I have submitted have not been subject to any deficiencies and/or questions, it has come to my knowledge that many questions are being raised in their evaluation.
• A real nuisance is the latest proposed revisions on the QRD template, particularly in the PL part (and particularly in the undesirable effects part). The emphasis at several occasions to reflect the full info of the SPC will lead to even longer PLs that are less readable. Considerations might be done to separate the liability (informed consent) issue from the package leaflet. Maybe have the key safety information relevant for the patient in a PL with an asterisk (*) note saying the full information can be found under a link or at the pharmacy, similar to the German AGBs
• I am responsible mainly for CMC documentation therefore implementation of any requirements regarding the SmPC or similar are not of my principle business.

Comments by Participants
• In terms of user testing assessment/requirements, there is huge inconsistency in 1/ the approach of different EU Competent Authorities and 2/ between different assessors in the same Competent Authority. This makes it very difficult for MA holders to judge what is and is not acceptable in leaflets (with one assessor or agency stating different opinions). More consistency should be encouraged. The Commission should also be encouraged to consider the importance of conveying the appropriate messages relating to benefit of medicines to the public, as well as risks, in order for the public to get a balanced and proportionate view in order to form their own opinions.
• A guideline on the understanding of key (safety) information is obviously needed to have a clear European legal framework especially nowadays where many packages are harmonised across Europe but member states point of views still not always harmonised.
• In the frame of my master thesis, I evaluated clinical studies and how and where related information is available. Does not matter whether it is a commercially available product or an IMP, I am not sure whether our patients always understand the offered information. Even in my circle of acquaintances and friends, medical terminology often causes confusion. Maybe we need three different levels of information: a. Short overviews for patients, b. More detailed information provided on generally known internet portals and c. Information for professionals (doctors, authorities, industry).*)
• We produce homeopathic medicinal products with purely national marketing authorizations or registrations. In Germany they do not need a SmPC. I am currently not aware of any new requests from other national authorities. By the way, it was not easy for me to generally decide what I would consider as key (safety) information in section 8 of the questionnaire. You easily end up checking all boxes as important. Therefore, as suggested in section 10 of the questionnaire, it makes sense to agree upon this with colleagues from reg. affairs, phv and clinical and also taking the relevant mp into consideration

***)** Original text was provided in German but translated into English

Table 5: Comments by Participants

5 Discussion

5.1 Importance of Key (Safety) Information in User Testings

As presented in 2.4 Key (Safety) Information – Legal Definition, the importance of detecting key (safety) messages of a medicinal product and covering them within the questionnaire of a target population's consultation is stressed in several guidance documents. The importance is even more emphasised in the context of similarity of key (safety) information between two medicinal products being mandatory for bridging of user tests.

In this survey more than 2/3 of the submitted readability user testings were full tests but only about 1/3 were bridging reports (4.2 Background Information on Submitted User Testings).

In general, the tests were accepted by the CA at a very high percentage, and only twice a deficiency related to lack of definition / coverage of key (safety) messages was detected - see 4.2.3 Acceptance of User Testings by Competent Authorities.

There might be several reasons why so little findings on this important item were described - even though readability user tests are focussed on key (safety) messages:

1. 146 user testings in total is only a little number without statistical significance and may therefore not represent reality. For 19% (28) of those, no outcome is available yet which reduces the number to only 118 tests suitable for evaluation - see 4.2.3 Acceptance of User Testings by Competent Authorities.
2. Key (safety) messages might be even more essential for bridging reports. The number of this kind of reports is even smaller, but it might increase in the future, due to an increasing number of user test submissions and consequentially, leading to an increase of bridgings to already performed tests.
3. The deficiencies may have been underreported in the survey. Only 12% of the user testings were accepted with findings and none rejected. Therefore, maybe some participants omitted to choose the option "deficiencies", as the submissions were approved, anyway - see 4.2.3 Acceptance of User Testings by Competent Authorities.
4. 25% of the target population consultations (4.2.2 Reasons for the Conduction of User Testings) were conducted in the UK based on the local legal requirement (2.2 United Kingdom's Legal Requirement of User Testings) with strict timelines for implementation and therefore causing a high workload for both the agency and the pharmaceutical industry. In the survey, one (1) case was reported where the same user testing for one medicinal product was accepted by MHRA locally, but a deficiency letter was issued for the harmonisation of the PL for the same product during the following renewal procedure with MHRA as Reference Member State. Lack of definition of key (safety) message was the critical finding and the user test was requested to be re-done. This represents the inconsistency of handling key

(safety) information as assessment criterion and may also lead to some biases in the determined deficiency reasons.

However, the importance of key (safety) messages still remains out of question when considering all guidance documents on user tests as well as the most current information on the *MHRA website/User testing of patient information leaflets/Changes to the assessment process in the Patient Information Quality Unit (Apr 2008)*, providing the following information:

"Assessment is focused on key areas of the leaflet to ensure that key messages for safe use in line with current clinical practice are included and displayed prominently."

5.2 Defining Key (Safety) Information in Daily Practice

Clearly, it is of paramount importance to define the key (safety) information of medicinal products upfront for the conduction of target population's consultations.

In this survey, 97% of the tests were conducted externally (4.2.4 Parties Performing User Testings). As shown in 4.2.5 Acceptance depending on Performing Party, the largest group of the pharmaceutical companies (28%) **trusted in the performance** of the party conducting the user tests and a few subjects also emphasised close co-operation with the user testing companies on that matter. This highlights the importance for the pharmaceutical industry to choose a reliable, well performing user testing company, preferably with experience in the indication area of the medicinal product to be tested and a with proof for their successful submissions to competent authorities. It is crucial to take some time for the decision which consultants should be chosen, to ask for offers and their reputation. For "specific" medicinal products or indications it should also be considered, whether the consultant already has experience in this area. It may be also helpful to ask colleagues for their preferences and recommendations on user testing companies.

18% **defined** the key (safety) information **in advance** and **provided it to the parties** conducting the tests and 13% **checked the coverage in the questionnaire before conduction of the tests** (4.2.5 Acceptance depending on Performing Party). This shows that the process of defining the key (safety) messages for a medicinal product is vital, too. As indicated in section 4.3.4 Parties to Be Involved into Definition, the largest group named by the participants on the survey was Regulatory Affairs (33%), followed by Pharmacovigilance (28%) and Clinical (23%). An extensive list of further "other parties" was also retrieved. This indicates that the choice of parties to be engaged might be a case-by-case decision. I would recommend setting up a task force for this purpose which may also be an assignment for Labelling Groups which might already be state-of-the-art in some companies.

5.2.1 Definition in Attendee's Own Words

Various ideas were expressed to answer Question 7 "How do you define 'key information/key safety information' in your own words?" (4.3.2 Definition in Attendee's Own Words - for the details please refer to Annex 3). All answers to this question were classified into two (2) categories:

1. General Definition of the Term "Key (Safety) Information

2. General Definition including Examples & PL Sections

Generally, the ideas of participants were widely spread, however, statements which were mentioned by several people were considered for evaluation.

1. General Definition of the Term "Key (Safety) Information

The majority of participants (68%) gave a general definition of the term and were therefore categorised into this group.

To establish a definition, about half of the attendees in this group (17) stressed the common driving principle that:

- Key information or key (safety) information is the **necessary information for the patient to use the medicinal product effectively, safely and appropriately**.

The second largest number (11) of contributors defined key (safety) information as:

- **Information about the risks associated with the medicine.** Only a few participants mentioned the aspect of **preventing these risks** in this context.

Some attendees even defined key (safety) information as:

- **Information** that **needs to be understood by the patient** and should be **patient-friendly** described. This spotlights that the comprehensibility of key (safety) information is of high importance.

A few participants pointed out that there are the two sides of core (safety) messages to be considered, namely risk AND benefit:

- On one hand it should minimise any **potential risk** to their safety and on the other hand it should maximise the **potential benefit** they will receive from the product.
- The important information to be **known before/during use** and also the one on what to do and whom to contact in case of any **safety-related problems** like side effects, interactions or overdose.

2. General Definition including Examples / PL Sections

32% of the contributors gave a general definition and/or combination with concrete examples mostly reflecting the PL sections like "contraindications" or "side effects".

Half of those (16%) gave a combination of both: a general definition and examples; the other half (16%) only gave concrete examples.

In this group, the general definition of key (safety) information was mostly very vaguely expressed as "important/essential information". This was probably because the definition was supported by the examples. The stronger general definitions which were similar to those discussed in the first group. Therefore, in this group the focus is put on the evaluation of the given examples.

The mostly mentioned examples were:

- Side effects (13)
- Warnings (11)
- Indications (10)

- Dosage (9)
- Contraindications (8)
- Interactions (7)
- Application (7)

In this category, the target was mainly put on the risks. This differs from the first group, where the benefit ("safe and correct use") was named by more participants than the risks.

Further examples given with less than five (5) mentions were not considered as meaningful for the definition. These were: Storage conditions, expiry date, overdose, special patient groups, precautions, name of product.

The examples of the evaluation above mainly correspond to the PL sections classified as key (safety) information in any case in Question 8 of the questionnaire - see 5.2.3 Classification of PL Sections.

5.2.2 Comparison with Definition from Regulatory Guidance Documents

Within this section the goal is to compare the results of this survey with the legal guidance documents available - see also 2.4 Key (Safety) Information – Legal Definition:

"Readability Guideline" / Guidance on the User Testing of Patient Information Leaflets

The *"Readability Guideline" (Rev. Jan 2009)* as well as in the *Guidance on the User Testing of Patient Information Leaflets (Jun 2005)* define key messages for user testings in two (2) ways:

Via definition of the key (safety) information to be covered by the questions of the user test questionnaire:

- Specific issues for safe and effective use
- Serious/critical/significant safety issues
- Can be found and understood so that the medicine can be used safely

Via the following PIL sections to be considered:

- Significant side effects
- Warnings
- Indications
- How to take/use the product

CMDh/100/2007 - Recommendations for Bridging

A similar general definition can be derived from *CMDh/100/2007*:

The questionnaire should address key messages and provide evidence that the readers of the PL can find and understand these messages and act appropriately so that the medicine can be used safely.

Always Read the Leaflet

The guidance document *Always Read the Leaflet* is not concerned with user testings themselves but nevertheless provides information about key messages to be included when drafting a PL in the concept of headline information. It states that key information should be the

- *"Most essential messages, bearing in mind the product and its context"*, summarised in two (2) to six (6) bullet points, should be kept short and should not replace reading the entire PL.

Furthermore, the following examples/PL sections are given:

- Why the patient should take the product
- The maximum dose or duration of treatment
- Potential side effects/withdrawal reactions (symptoms to look out for, especially for common or serious side effects)
- Contraindications
- Important drug interactions
- Circumstances in which the drug should be stopped
- What to do if the medicine doesn't work
- Where to find further information

The paraphrases in the four guidance documents were similar and were also covered by the attendee's own definitions. However, these definitions were more detailed and descriptive – see Table 6:

Questionnaire (Definition in Attendee's Own Words)	**"Readability Guideline" / Guidance on the User Testing of Patient Information Leaflets**	**Always Read the Leaflet**
"Important/essential information"	-	*"Most essential messages, bearing in mind the product and its context"*, summarised in two (2) to six (6) bullet points, should be kept short and should not replace reading the entire PL.
Key information or key (safety) information is the necessary information for the patient to use the medicinal product effectively, safely and appropriately.	Specific issues for safe and effective use	-
Information about the risks associated with the medicine. Only a few participants mentioned the aspect of preventing these risks in this context.	Serious/critical/significant safety issues	-
Information that needs to be understood by the patient and…	Can be found and understood so that the medicine can be used safely	-
…should be patient-friendly described.	-	-

Questionnaire (Definition in Attendee's Own Words)	"Readability Guideline" / Guidance on the User Testing of Patient Information Leaflets	Always Read the Leaflet
Information that should minimise any potential risk to their safety and on the other hand it should maximise the potential benefit they will receive from the product.	-	-

Table 6: General Definition: Comparison Elaborated Definition vs. Legal Definition

The general definitions of the questionnaire were again very similar to those in the ***„Readability Guideline" / Guidance on the User Testing of Patient Information Leaflets.*** The definition given in the document ***Always Read the Leaflet*** is vaguer, similar to what the second group of answers to the questionnaire stated, who combined the definition with examples.

The reason might be that the document ***Always Read the Leaflet*** is more focused on clear and detailed examples than the other documents.

In conclusion, to elaborate a definition regardless whether out of regulatory documents or from the questionnaire, a combination of general definition or practical examples should be used.

The examples for key (safety) information are similar in the three (3) guidance documents *"Readability Guideline", Guidance on the User Testing of Patient Information Leaflet*s and *Always Read the Leaflet* but none is given in *CMDh/100/2007 - Recommendations for Bridging* – see Table 7:

Questionnaire (Definition in Attendee's Own Words)	"Readability Guideline" / Guidance on the User Testing of Patient Information Leaflets	Always Read the Leaflet
Warnings	Warnings	Circumstances in which the drug should be stopped
Side effects	Significant side effects	Potential side effects/withdrawal reactions (symptoms to look out for, especially for common or serious side effects)
Indications	Indications	Why the patient should take the product
Contraindications	-	Contraindications
Dosage	-	The maximum dose or duration of treatment
Interactions	-	Important drug interactions
Application	How to take/use the product	-

Table 7: Examples: Comparison Elaborated Definition vs. Legal Definition

In the guidance document *Always read the leaflet*, the emphasis is more on the creation of the PL than on user testings. Therefore it is not surprising that some aspects appear in this document but were not mentioned either by the attendees of the questionnaire or by the other regulatory guidance documents focusing on user testings.
These are:

- What to do if the medicine doesn't work
- Where to find further information

Remark: "Where to find further information" can be disregarded as this means only that the headline information should provide a reference to the PL for more information. "What to do if the medicine doesn't work" was also not considered as there is currently no PL section in the QRD template dedicated to this content but it might be added to "warnings".

In conclusion, the PL example sections selected for the definition of key (safety) information for user testing via this survey cover all PL sections mentioned in the guidance documents.

Conclusion: Definition of Key (Safety) Information in User Testings

One should consider that on one hand, a definition providing very detailed and precise examples might not fit well for all products, on the other hand a general definition leaves the decision what to categorise as key (safety) information with the company, which will naturally result in different opinions.

Therefore, the definition should be a well balanced combination of a general definition and examples. The following definition was compiled from the available legal guidance documents and the survey:

Key (safety) information in user testings is defined as:

1. **Necessary information for the patient to use the medicinal product effectively, safely and appropriately.**
2. **Information about the risks associated with the medicine.**
3. **Information that needs to be understood by the patient / presented in patient-friendly way.**
4. **Information that should minimise any potential risk and maximise the potential benefit of a medicinal product.**
5. **"Important/essential information", e.g.**
    - **Warnings**
    - **Side Effects**
    - **Indications**
    - **Contraindications**
    - **Dosage**
    - **Interactions**
    - **Application**

5.2.3 Classification of PL Sections

Not only the most prominent example PL sections were selected for the definition of key (safety) information also all PL sections were categorised. To analyse which sections of the PL are considered to contain key (safety) information, the following classes were to be selected:

- YES – in any case
- YES – depending on the medicinal product
- NO

See 4.3.3 Classification of PL Sections for further details.

To analyse the outcome of this survey, the following categorisation criteria were defined:

1. **YES – in any case:**
   - Classified when at least an average of 80% of the participants agreed on it AND both groups (experienced and un-experienced contributors) were above 60%.
2. **YES – depending on the medicinal product:**
   - Categorised when the conditions of category 1 "YES – in any case" were not met AND "YES – depending on the medicinal product" was the next highest percentage.
3. **NO:**
   - Chosen when the conditions of category 1 "YES – in any case" were not met AND "NO" is the next highest percentage.

   OR
   - "NO" with at least an average of 80% of the participants agreed on it AND both groups (experienced and un-experienced contributors) were above 60%.

Generally, the party without user testing experience chose the strongest key (safety) information category "YES – in any case" with a much higher preference than the by experienced colleagues – see 4.3.3 Classification of PL Sections. Due to less experience, these colleagues might be more doubtful of their decision and therefore act more cautious with a higher need on security. However, their opinion is relevant for this evaluation to border and to verify the classification of the experience ones. Therefore the un-experienced group was included into the analysis and the above rules were established in order to obtain clear results - as presented in Table 8: The percentages given are the average of all participants; the shaded fields represent the category into which the PL section falls (see 4.3.3 Classification of PL Sections).

	YES – in any case	**YES - but depending on medicinal product**	**NO**
Indication(s)	88%	10%	2%
Contraindication(s)	98%	2%	0%
Warning(s)	95%	5%	0%
Interaction(s)	81%	19%	0%
Pregnancy/Lactation	80%	20%	0%
Dosage	87%	12%	2%
Application	59%	31%	10%

	YES – in any case	YES - but depending on medicinal product	NO
Special Patient Group(s)	46%	53%	2%
Duration of Usage	66%	31%	3%
Overdosing	64%	34%	2%
Omission to Use/Take Medicine	55%	43%	2%
Stop Using/Taking Medicinal Product	60%	40%	0%
Side Effect(s)	95%	5%	0%
Storage Conditions	49%	46%	5%
Expiry	51%	16%	33%
Composition of Medicinal Product	45%	22%	33%
Appearance of Medicinal Product	28%	40%	32%
Pack Size(s)	4%	19%	77%
Marketing Authorisation Holder	19%	2%	79%
Manufacturer(s)	5%	4%	91%
Date of Revision/Approval of Leaflet	13%	2%	85%
Legal Status	10%	21%	69%

Table 8: Sections of PL to Be Considered as Key (Safety) Information

Remark: Furthermore, it was noted that for the categories “YES – but depending on medicinal product” and “NO” more comments were given by the participants as for a clear decision on “YES – in any case” - see 4.3.3 Classification of PL Sections. It is obvious that “YES – but depending on medicinal product” needs further explanation.

Following the evaluation of the collected data, my intention was to summarise the outcome of the survey in a concise practical recommendation on the conduction of user testings (see 5.4 Recommendations for Practice).

This included an instruction on where to find key (safety) information in the PL, based on the classification results (Table 8). This table might be used by pharmaceutical industry for defining key (safety) information of a specific medicinal product. For practical reasons, the classification results were incorporated into the PL structure following the currently effective QRD template (*http://www.ema.europa.eu/htms/ human /qrd/qrdtemplate.htm*) - see Table 9.

The meaning of the terms like “application”, “expiry” etc. used in the survey (4.3.3 Classification of PL Sections) were further explained via the information available in the annotated QRD template in order to ensure clear understanding. These suggestions were strengthened by the comments presented in 4.3.3 Classification of PL Sections.

GREEN	**key (safety) information - in any case**
YELLOW	**key (safety) information - but depending on medicinal product**
RED	**NO key (safety) information**

QRD Template	Terms from Survey
PACKAGE LEAFLET: INFORMATION FOR THE USER	
1. What X is and what it is used for *"[Therapeutic indications]"*	**Indication(s)**
2. Before you <take> <use> X **Do not <take> <use> X** *"[…absolute contraindications …, including contraindications due to interactions with other medicinal products. Other precautions and special warnings should be made in the next section…"]*	**Contraindication(s)**
Take special care with X *"[Appropriate precautions for use; special warnings]"*	**Warning(s)**
<Taking> <Using> other medicines *"[Interactions with other medicinal products]"* **<Taking> <Using> X with food and drink** *"[Interactions with food and drink]"*	**Interaction(s)**
Pregnancy and breast-feeding *"[Use by pregnant or breast-feeding women]"*	**Pregnancy and Lactation**
Driving and using machines *"[Effects on the ability to drive or to use machines] "*	**Warning(s)**
Important information about some of the ingredients of X *"[Excipients warnings]"*	**Warning(s)**
3. How to <take> <use> X *"[Dosage. (SmPC section 4.2)]"*	**Dosage**
<Use in children> Remark: Usually "elderly patients", "renal/liver impairment", "particular genotype" etc. are also presented under this sub header (see "*SmPC Guideline" (Rev. Sept 2009)*)	**Special Patient Group(s)**
"[Method and/or route(s) of administration]"	**Application**
"[Frequency of administration]"	**Dosage**
"[Duration of treatment]"	**Duration of Usage/Intake**
If you <take> <use> more X than you should *"[Symptoms in case of overdose and actions to be taken.]"*	**Overdosing**

QRD Template	Terms from Survey
PACKAGE LEAFLET: INFORMATION FOR THE USER	
If you forget to <take> <use> X *"[Actions to be taken when one or more doses have been missed]"*	**Omission to Take/Use Medicine**
If you stop <taking> <using> X *"[Indication of the risk of withdrawal effects]"*	**Stop Using/Taking Medicinal Product**
4. Possible side effects *"[Description of side effects]"*	**Side Effect(s)**
5. How to store X *"[Expiry date]"*	**Expiry**
"[Storage conditions]"	**Storage Conditions**
"[Where applicable, shelf life after reconstitution, dilution or after first opening the container]"	**Expiry**
"[Where appropriate, warning against certain visible signs of deterioration]"	**Appearance**
6. Further information **What X contains** *"[Full statement of the active substance(s) and excipient(s)] "*	**Composition of Medicinal Product**
What X looks like (and contents of the pack) *"[Pharmaceutical form, nature and contents of container in weight, volume or units of dosage]"*	**Appearance**
(What X looks like and) **contents of the pack** *"[Pharmaceutical form, nature and contents of container in weight, volume or units of dosage]"*	**Pack Size(s)**
Marketing Authorisation Holder and Manufacturer *"[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]"*	**Marketing Authorisation Holder** **Manufacturer(s)**
This leaflet was last approved in {MM/YYYY} *"[Date of granting of the Marketing Authorisation/approval of latest variation or transfer,…]"*	**Date of Revision/Date of Application**

QRD Template	Terms from Survey
PACKAGE LEAFLET: INFORMATION FOR THE USER	
Remark: Legal status is not part of PL according to QRD but included in countries like Germany	**Legal Status**

Table 9: Classification of QRD Template with Regard to Key (Safety) Information

5.2.4 Possible Weaknesses of Survey

A possible weakness of the survey may be reflected via one (1) comment given by an un-experienced attendee (see 4.5 Comments by Participants): "By the way, it was not easy for me to generally decide what I would consider as key (safety) information in section 8 of the questionnaire. You easily end up checking all boxes as important…". This reflects the outcome of the classification of PL sections that un-experienced participants chose much more often the category key (safety) information in any case than the experienced – see 5.2.3 Classification of PL Sections.

Some remarked that specific PL sections are only relevant information for healthcare professionals or are only key (safety) information for user tests in case the medicine is administered by the patients themselves. It seems that here was some misunderstanding of two essential principals:

1. Patients are today proactive and more empowered consumers of health care who's unequal access to information should be strengthened more and more (*EC, MEMO: Information to patients on prescription-only medicinal products (Dec 2008)*)
2. PLs are mandatory product information's elements for all medicinal products licensed (*Directive 2001/83, Article 58*) and as such accessible information for the patients but also for healthcare professionals like nurses in the hospital who in urgent situations have quick access to the PL but maybe not to the SmPC.

These remarks were all given by participants without user testing experience. This also brings up the question whether it should have been ensured that all subjects of this survey have similar knowledge for getting consistent results, and whether only experienced participants should have been involved. However, as outlined in 5.2.3 Classification of PL Sections, I consider the opinion of the un-experienced colleagues as meaningful to border and verify the opinion of the experienced.

5.3 General Relevance of Key (Safety) Information

Not only the requirement of Article 59 (3) on target population's consultation but also the ongoing discussions on the EU Pharma Package and communication to patients as well as the updated "*SmPC Guideline" (Rev. Sept 2009)* emphasise the increasing demand from pharmaceutical industry to get aware of the key (safety) information of their medicinal product, define it and decide how to communicate it. With the little awareness of the ongoing discussions (see 4.4 Current Discus-

sions - Key (Safety) Information), it seems there is room for improvement here and especially a need to spotlight the importance of this task.

5.4 Recommendations for Practice

Following the evaluation of the data collected, the intention was to summarise the outcome of the survey in a concise recommendation on the conduction of user testings for pharmaceutical companies. In the survey, it was clearly shown that almost all (97%) of the companies have their user testings performed by third parties, i.e. consultants specialised on user testings. However, even when outsourced to specialists, there are still some responsibilities with the pharmaceutical company. Therefore, this recommendation is focused on the activities to be carried out by the pharmaceutical company in addition to the work of the consultant carrying out the user testing. For the conduct of user tests including the definition of key (safety) messages for a specific medicinal product, I would give the following recommendations as Good Regulatory Practice for the conduct of readability user testings to pharmaceutical industry:

1. **Settle a taskforce on labelling of medicinal products** consisting of members of different functions like Regulatory, Pharmacovigilance, Clinical etc. (see also 5.2 Defining Key (Safety) Information in Daily Practice) with regular meetings held.

   The responsibilities of such "Labelling Boards" might be writing and updating the product information but also defining key (safety) information for a medicinal product in general and for readability user testings specifically. They should also be involved in setting up the questions for readability tests. A related task might be taking care of Pharmacovigilance topics like the Reference Safety Information as well as the Core Safety Profile of medicines – see *Guidance Document for Marketing Authorisation Holders on Submissions of PSURs under the EU PSUR Work Sharing Scheme (Nov 2009)*.

2. **Define key (safety) messages of a medicinal product's PL:** Under consideration of the definition developed in 5.2.1 Definition in Attendee's Own Words, it is recommended to classify the sections of the PL in regard to key (safety) information as follows:

   "Key (safety) information – in any case":

   - Indication(s)
   - Contraindication(s)
   - Warning(s)
   - Interaction(s)
   - Pregnancy/Lactation
   - Dosage
   - Side Effect(s)

   "Key (safety) information – depending on the medicinal product":

   - Application
   - Special Patient Group(s)
   - Duration of Usage
   - Overdosing
   - Omission to Use/Take Medicine
   - Stop Using/Taking Medicinal Product

- Storage Conditions
- Appearance of Medicinal Product

To ease the classification, a Table 9 was elaborated via this survey which can be used as working tool for that purpose.

3. **Define questionnaire for user testing:** As outlined in the "*Readability Guideline" (Rev. Jan 2009)*, the questions should adequately cover the key (safety) messages of the medicine and should be usually 12 -15 questions and the questionnaire should "cover a balance of general and specific issues". Based on the outcome of the survey (5.2.3 Classification of PL Sections), the recommendation is that 1 to 2 questions should be chosen per PL section classified as "key (safety) information – in any case".

   These will be completed on case-by-case basis by questions focussed on the sections categorised as "key (safety) information – depending on the medicinal product".

4. **Choice of appropriate user testing company:** The choice of the consultant to be taken is of utmost importance. It is recommended to choose a reliable, well performing company with successful submissions to Competent Authorities, at best with experience in the indication area of the medicinal product to be tested – see for details 5.2 Defining Key (Safety) Information in Daily Practice.

5. **Close cooperation with user testing company:** For the procedural steps 2 and 3 (above) it is mandatory to work hand in hand with the chosen consultant in order to achieve the best result.

6. Highly recommended for people without user testing experience to **involve someone with experience** for the definition of the key (safety) information of a medicinal product. This is based on the outcome of 5.2.3 Classification of PL Sections.

5.5 Comments for Consideration

I selected some comments by participants of this survey (see 4.5 Comments by Participants) on which further consideration and discussion may be useful:

1. "After almost 5 years following implementation of the revised legislation, user testing still appears to be only a formal requirement. In my opinion, submissions are only checked for completeness in this regard. Following revisions of the SmPC / PL, no update of the user testing was requested so far from an authority."

2. "In terms of user testing assessment/requirements, there is huge inconsistency in 1/ the approach of different EU Competent Authorities and 2/ between different assessors in the same Competent Authority. This makes it very difficult for MA holders to judge what is and is not acceptable in leaflets (with one assessor or agency stating different opinions). More consistency should be encouraged."

These two comments suggest the need for a more consistent and obvious way of user testing assessment as well as a clearly recognisable improvement of the readability. There might be room for improvement for CAs with this regard.

3. “A real nuisance is the latest proposed revisions on the QRD template, particularly in the PL part (and particularly in the undesirable effects part). The emphasis at several occasions to reflect the full info of the SPC will lead to even longer PLs that are less readable.”

This colleague is referring to *EMA, QRD Annotated Template: Revision of the Product Information, Draft 1 (Feb 2010)* which was for external consultation by 03 May 2010. We will see how the final decision on the updated QRD templates will be and which impact this will have on PL in our daily practice. However, it is out of discussion that it will be challenging to maintain the balance between complete information and readability for the patients.

4. “Considerations might be done to separate the liability (informed consent) issue from the package leaflet. Maybe have the key safety information relevant for the patient in a PL with an asterisk (*) note saying the full information can be found under a link or at the pharmacy, similar to the German AGBs”

5. „Maybe we need three different levels of information: a. Short overviews for patients, b. More detailed information provided on generally known internet portals and c. Information for professionals (doctors, authorities, industry).”

   [Remark: Was only provided in German but translated into English]

   These two notes were related to the current discussion on patient information within the frame of the EU Pharma Package and provides some ideas from pharmaceutical industry on this matter (*EC, MEMO: Information to patients on prescription-only medicinal products (Dec 2008)*).

6. „The Commission should also be encouraged to consider the importance of conveying the appropriate messages relating to benefit of medicines to the public, as well as risks, in order for the public to get a balanced and proportionate view in order to form their own opinions.”

   We might be more focused on the risks than on benefits; this is driven by the requests from agencies and by our daily work. This is reflected by the comment 6 above. However, the need to emphasise the benefit of a medicinal product for patient’s compliance has already been taken into account within the “SmPC Guideline” (Rev. Sept 2009) and its revised content.

7. “A guideline on the understanding of key (safety) information is obviously needed to have a clear European legal framework especially nowadays where many packages are harmonised across Europe but Member States point of views still not always harmonised.”

This remark may emphasise a need for a clear definition of key (safety) messages for regulatory’s daily practice similarly to the *Guideline on the Definition of a Potential Serious Risk to Public Health in the Context of Article 29(1) and (2) of Directive 2001/83/EC (Mar 2006).*

6 Conclusion and Outlook

For a successful user testing it is mandatory to define key (safety) information of a medicinal product. The key (safety) information of a medicine differs from one medicinal product to another and will change during a product's lifecycle. Therefore, this definition must constantly be redefined by marketing authorisation holder. In the regulatory environment there is currently no clear legal definition available but with the results of this master thesis a compiled definition and a recommendation for Good Regulatory Practice is offered (see 5.4 Recommendations for Practice).

Further development of the results of this master thesis possibly ending up in a guideline to define key (safety) information in general or specifically for user testings might be a future project for Competent Authorities in collaboration with stakeholders.

7 Summary

All medicinal products are required by *Article 54, Article 55 and Article 59 of Directive 2001/83/EC* to be accompanied by outer/inner labelling text and a package leaflet setting out comprehensive information which is accessible to and understandable by those who receive it, so that they can use their medicine safely and appropriately [...].

Article 63(2) of Directive 2001/83/EC also requires 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 [...].

Article 59(3) of Directive 2001/83/EC provides that the package leaflet shall reflect the results of consultations with target patient groups to ensure the requirements of *Article 63(2)* are met.

The topics of this masterwork are:

- To investigate the importance of "key (safety) information" for the submission of readability user testings via a questionnaire
- To evaluate the background information on regulatory submissions of readability user testings
- To study how colleagues define the expression "key (safety) information" in their daily regulatory practice
- To investigate on further importance of this term with regard to current ongoing discussions in the regulatory environment.

Furthermore, the goal is to elaborate a definition of the term "key (safety) information" and recommendations for the pharmaceutical industry how to handle "key (safety) information" in readability user testing appropriately considering both the results from the questionnaire and the available guidance documents.

Conduction of the Survey

In order to evaluate how pharmaceutical companies define „key (safety) information“ in their daily practice, a survey was conducted via a questionnaire sent out to approximately 200 colleagues working in Regulatory Affairs throughout Europe.

Sixty (60) responses on the final questionnaire have been received for evaluation and discussion within this master thesis. Half of the attendees (30) had at least one (1) user test performed/submitted. Experienced and un-experienced participants were categorised into two (2) subgroups for evaluation. Out of 146 user testings submitted, 46 (32%) were bridging reports and 100 (68%) were full tests.

The majority of user testings was performed in relation to first marketing authorisation application of a medicinal product (43%), due to local national requirement in the UK (25%), other significant text changes (12%) and renewal (10%).

In general, the tests were accepted by the Competent Authorities at a very high percentage: 65% were accepted without deficiencies, 12% were accepted with deficiencies, and only twice a deficiency related to lack of definition / coverage of key (safety) messages was detected.

Definition of Key (Safety) Information

The importance of key (safety) messages still remains out of question when considering all guidance documents on user tests.

Not only the requirement of Article 59 (3) on target population's consultation but also the ongoing discussions on the EU Pharma Package and communication to patients as well as the updated "*SmPC Guideline" (Rev. Sept 2009)* emphasise the increasing demand from pharmaceutical industry to get aware of the key (safety) information of their medicinal product, define it and decide how to communicate it.

Clearly, it is of paramount importance to define the key (safety) information of medicinal products upfront for the conduction of target population's consultations.

A definition of "key (safety) information" is paraphrased in a complex way and spread over many text passages in several legal guidance documents, but no compiled definition is given.

It was determined that the definition should be a well balanced combination of a general definition and examples. The following definition was compiled from the available legal guidance documents and the survey:

Key (safety) information in user testings is defined as:

6. Necessary information for the patient to use the medicinal product effectively, safely and appropriately.
7. Information about the risks associated with the medicine.
8. Information that needs to be understood by the patient / presented in patient-friendly way.
9. Information that should minimise any potential risk and maximise the potential benefit of a medicinal product.
10. "Important/essential information", e.g.
    - Warnings
    - Side Effects
    - Indications
    - Contraindications
    - Dosage
    - Interactions
    - Application

Recommendations for Practice

In the survey, it was clearly shown that almost all (97%) of the companies have their user testings performed by third parties, i.e. consultants specialised on user testings. Therefore, this recommendation is focused on the activities to be carried out by the pharmaceutical company in addition to the work of the consultant carrying out the user testing. For the conduct of user tests including the definition of key (safety) messages for a specific medicinal product, I would give the following recommendations as Good Regulatory Practice for the conduct of readability user testings to pharmaceutical industry:

1. **Settle a taskforce on labelling of medicinal products** consisting of members of different functions like Regulatory, Pharmacovigilance, Clinical etc. with regular meetings held. The responsibilities of such "Labelling Boards" might be writing and updating the product information but also defining key (safety) information for a medicinal product in general and for readability user testings specifically. They should also be involved in setting up the questions for readability tests. A related task might be taking care of Pharmacovigilance topics like the Reference Safety Information as well as the Core Safety Profile of medicines.

2. **Define key (safety) messages of a medicinal product's PL:** Under consideration of the definition developed, it is recommended to classify the sections of the PL in regard to key (safety) information as follows.

   "Key (safety) information – in any case":

   - Indication(s)
   - Contraindication(s)
   - Warning(s)
   - Interaction(s)
   - Pregnancy/Lactation
   - Dosage
   - Side Effect(s)

   "Key (safety) information – depending on the medicinal product":

   - Application
   - Special Patient Group(s)
   - Duration of Usage
   - Overdosing
   - Omission to Use/Take Medicine
   - Stop Using/Taking Medicinal Product
   - Storage Conditions
   - Appearance of Medicinal Product

   To ease the classification, a table was elaborated via this survey which can be used as working tool for that purpose.

3. **Define questionnaire for user testing:** As outlined in the **"***Readability Guideline" (Rev. Jan 2009)*, the questions should adequately cover the key (safety) messages of the medicine and should be usually 12 -15 questions and the questionnaire should "cover a balance of general and specific issues". Based on the outcome of the survey, the recommendation is that 1 to 2 questions should be chosen per PL section classified as "key (safety) informa-

tion – in any case". These will be completed on case-by-case basis by questions focussed on the sections categorised as "key (safety) information – depending on the medicinal product".

4. **Choice of appropriate user testing company:** The choice of the consultant to be taken is of utmost importance. It is recommended to choose a reliable, well performing company with successful submissions to Competent Authorities, at best with experience in the indication area of the medicinal product to be tested.
5. **Close cooperation with user testing company:** For the procedural steps 2 and 3 (above) it is mandatory to work hand in hand with the chosen consultant in order to achieve the best result.
6. Highly recommended for people without user testing experience to **involve someone with experience** for the definition of the key (safety) information of a medicinal product.

Outlook

Further development of the results of this master thesis possibly ending up in a guideline to define key (safety) information in general or specifically for user testings might be a future project for Competent Authorities in collaboration with stakeholders.

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MHRA, **Guidance on the User Testing of Patient Information Leaflets** (Jun 2005)

Annex 1: Pilot Questionnaire

PILOT QUESTIONNAIRE

A. Readability User Testings

1. How many readability user testings have you already submitted to an agency?

Please provide number:

2. How many of these testings have been bridging reports?

Please provide number:

3. Have these testings (incl. bridging reports) been accepted without deficiencies?

☐ Yes

☐ No - if no, how many have not been accepted?

Please provide number:

Please specify reason(s) for non-acceptance:

4. What was/were the reason(s) for the requirement of your user testings (incl. bridging reports) for your medicinal product(s)?

The "Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products" as of January 2009 lists several reasons for the requirement of user testings. Please choose one or more of the following possible reasons:

☐ ***First authorisation of a medicinal product with a new active substance***

Please provide number of user testings conducted for this reason:

☐ ***Medicinal products with a new presentation, e.g. new pharmaceutical form, new patient group***

Please provide number of user testings conducted for this reason:

☐ ***Change in legal status***

Please provide number:

☐ ***Particular critical safety issues***

Please provide number of user testings conducted for this reason:

☐ ***Other significant text changes***

Please provide number of user testings conducted for this reason:

What changes have been considered as “significant text changes”?

Please specify:

☐ ***Other reasons (e.g. layout changes)***

Please specify reason(s):

Please provide number of user testings conducted for this reason:

5. <u>How</u> have your user testings (incl. bridging reports) been conducted?

Please tick one or more boxes.

☐ ***Externally*** (conducted by consultant specialised on user testings)

Please specify number of user testings:

☐ ***Internally*** (conducted by company’s function/department specialised on user testings)

Please specify number of user testings:

☐ ***Other (e.g. you work at a consultant specialised on user testings)*** – please specify details:

Please specify number of user testings:

6. <u>Acceptance by agencies</u> per parties performing the user testings (incl. bridging reports)

6.1 How many of the <u>externally</u> performed user testings have not been accepted by the agencies

Consultant specialised on user testings – see question 5?

Please provide number:

6.2 How many of the <u>internally</u> performed user testings have not been accepted by the agencies?

Company’s department specialised on user testings – see question 5?

Please provide number:

6.3 How many of the <u>otherwise</u> performed user testings have not been accepted by the agencies?

Other – see question 5?

Please provide number:

7. Readability user testings are focused on the <u>key information/key safety information</u> of a medicinal product. How do you define *"key information/key safety information"* in your own words?

8. Which of the following would you classify as <u>key information/key safety information</u> to be considered for a questionnaire of a user testings? Please tick one or more boxes.

☐ Composition of medicinal product	☐ Special patient group(s)
☐ Side effect(s)	☐ Pack size(s)
☐ Indication(s)	☐ Contraindication(s)
☐ Manufacturer(s)	☐ Marketing Authorisation Holder
☐ Overdosing	☐ Interaction(s)
☐ Warning(s)	☐ Omission to use/take medicine
☐ Legal status	☐ Pregnancy/lactation
☐ Dosage	☐ Appearance of medicinal product
☐ Application	☐ Duration of usage
☐ Date of revision/approval of leaflet	☐ Stop using/taking medicinal product
☐ Expiration	**Comments:**
☐ Storage	

9. How did you ensure that the key information/key safety information for your medicinal product has been covered by the questionnaire of the user testings (incl. bridging reports)?

9.1 Please choose the following tick-boxes if the user testing(s) has/have been performed by an external company

☐ Trust in performance of the company performing the testing

☐ Defined the key information in advance and provided it to the company performing the testing

☐ Checked that key information has been covered after receipt of user testing report

☐ Other way of ensuring that key information has been covered – please specify:

9.2 Please choose the following tick-boxes if the user testing(s) has/have been performed internally (e.g. specialised department in your company)

☐ Trust in performance of the department performing the testing

☐ Defined the key information in advance and provided it to the department performing the testing

☐ Checked that key information has been covered after receipt of user testing report

☐ Other way of ensuring that key information has been covered – please specify:

9.3 Please choose the following tick-boxes if the user testing(s) has/have been performed otherwise (e.g. you work in a company specialised on user testings)

☐ Trust in performance of the party performing the testing

☐ Defined the key information in advance and provided it to the department performing the testing

☐ Checked that key information has been covered after receipt of user testing report

☐ Other way of ensuring that key information has been covered – please specify:

10. <u>What parties</u> have you involved/would you <u>involve in defining the key information/key safety information</u> of a medicinal product?

☐ Regulatory Affairs

☐ Pharmacovigilance

☐ Clinical

☐ Other party – please specify:

B. General

11. With the EU pharma package the EU commission targets to inform patients about the key information of medicinal products. Are you aware of these plans?

☐ No

☐ Yes – if yes have you already started considerations/actions/projects?

☐ No – if no, why not?

☐ Yes – if yes, please specify:

12. The new "Guideline on Summary of Products Characteristics" as of September 2009 asks to summarise the key safety information in section "4.8 Undesirable effects" / subsections "a. Summary of the safety profile" and "c. Description of selected adverse reactions". Are you aware of this requirement to be implemented in May 2010?

☐ No

☐ Yes – if yes have you already started considerations/actions/projects?

☐ No – if no, why not?

☐ Yes – if yes, please specify:

13. Your personal comments on this questionnaire

This questionnaire will be part of my master thesis.

Please note that this questionnaire will be handled and evaluated anonymously.

Thank you for your time and your support.

Annex 2: Final Questionnaire

QUESTIONNAIRE

A. Readability User Testings

1. **<u>How many readability user testings</u> have you already submitted to an agency?**

   Please provide number:

2. **<u>How many</u> of the testings of question 1 have been <u>bridging reports</u>?**

   Please provide number:

3. **Have these testings (incl. bridging reports) been <u>accepted without deficiencies</u>? Please choose one or more options.**

   ☐ **Accepted <u>without</u>** deficiencies

   Please provide number:

   ☐ **Accepted with** deficiencies

   Please provide number:

   ☐ **Rejected**

   Please provide number:

   ☐ **Deficiency letter** has been received but **procedure** still **pending**

   Please provide number:

   ☐ **Pre-assessment positive** but **procedure** still **pending**

   Please provide number:

   ☐ **Assessment** still **pending, no outcome** so far available

   Please provide number:

   Please specify the main reason(s) for deficiencies/non-acceptance:

4. What was/were the reason(s) for the requirement of your user testings (incl. bridging reports) for your medicinal product(s)?

The "Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products" as of January 2009 lists several reasons for the requirement of user testings. Please choose one OR more of the following possible reasons:

☐ ***First authorisation of a medicinal product with a new active substance***

Please provide number of user testings conducted for this reason:

☐ ***Medicinal products with a new presentation, e.g. new pharmaceutical form, new patient group***

Please provide number of user testings conducted for this reason:

☐ ***Change in legal status***

Please provide number of user testings conducted for this reason:

☐ ***Particular critical safety issues***

Please provide number of user testings conducted for this reason:

☐ ***Other significant text changes (e.g. harmonised labelling/package leaflet)***

Please provide number of user testings conducted for this reason:

What changes have been considered as "significant text changes"?

Please specify:

☐ ***Other reasons (e.g. layout changes, national local requirement)***

Please specify reason(s)	**Please provide number of user testings conducted for this reason**

5. How have your user testings (incl. bridging reports) been conducted? Please tick one or more boxes.

☐ ***Externally*** **(conducted by consultant specialised on user testings)**

Please specify number of user testings:

☐ ***Internally*** **(conducted by company's function/department specialised on user testings)**

Please specify number of user testings:

☐ ***Other (e.g. you work at a consultant specialised on user testings)*** – please specify "other":

Please specify number of user testings:

6. Acceptance by agencies per parties performing the user testings (incl. bridging reports)

6.1 How many of the externally performed user testings have caused deficiencies/have been rejected by the agencies

Consultant specialised on user testings – see question 5?

Please provide number:

6.2 How many of the internally performed user testings have caused deficiencies/have been rejected by the agencies?

Company's department specialised on user testings – see question 5?

Please provide number:

6.3 How many of the otherwise performed user testings have caused deficiencies/have been rejected by the agencies?

Other – see question 5?

Please provide number:

7. Readability user testings are focused on the <u>key information/key safety information</u> of a medicinal product. 

How do you define *"key information/key safety information"* in your own words?

8. Which of the following would you classify as <u>key information/key safety information</u> for a questionnaire of a user testing? Please tick one or more boxes.

	YES - in any case	**YES** - but depending on medicinal product	**NO**	**Comments**
Composition of medicinal product	☐	☐	☐	
Side effect(s)	☐	☐	☐	
Indication(s)	☐	☐	☐	
Manufacturer(s)	☐	☐	☐	
Overdosing	☐	☐	☐	
Warning(s)	☐	☐	☐	
Legal status	☐	☐	☐	
Dosage	☐	☐	☐	
Application	☐	☐	☐	
Date of revision/approval of leaflet	☐	☐	☐	
Expiry	☐	☐	☐	
Storage conditions	☐	☐	☐	
Special patient group(s)	☐	☐	☐	

	YES - in any case	**YES** - but depending on medicinal product	**NO**	**Comments**
Pack size(s)	☐	☐	☐	
Contraindication(s)	☐	☐	☐	
Marketing Authorisation Holder	☐	☐	☐	
Interaction(s)	☐	☐	☐	
Omission to use/take medicine	☐	☐	☐	
Pregnancy/lactation	☐	☐	☐	
Appearance of medicinal product	☐	☐	☐	
Duration of usage	☐	☐	☐	
Stop using/taking medicinal product	☐	☐	☐	

9. How did you ensure that the key information/key safety information for your medicinal product has been covered by the questionnaire of the user testings (incl. bridging reports)?

9.1 Please choose the following tick-boxes if the user testing(s) has/have been performed by an external company – see question 5

☐ Trust in performance of the company performing the testing

☐ Defined the key information in advance and provided it to the company performing the testing

☐ Checked that key information has been covered after receipt of user testing report

☐ Other way of ensuring that key information has been covered

– please specify:

9.2 Please choose the following tick-boxes if the user testing(s) has/have been performed internally (e.g. specialised department in your company) – see question 5

☐ Trust in performance of the department performing the testing

☐ Defined the key information in advance and provided it to the department performing the testing

☐ Checked that key information has been covered after receipt of user testing report

☐ Other way of ensuring that key information has been covered

– please specify:

9.3 Please choose the following tick-boxes if the user testing(s) has/have been performed otherwise (e.g. you work in a company specialised on user testings) – see question 5

☐ Trust in performance of the party performing the testing

☐ Defined the key information in advance and provided it to the department performing the testing

☐ Checked that key information has been covered after receipt of user testing report

☐ Other way of ensuring that key information has been covered

– please specify:

10. <u>What parties</u> have you involved/would you <u>involve in defining the key information/key safety information</u> of a medicinal product?

☐ Regulatory Affairs

☐ Pharmacovigilance

☐ Clinical

☐ Other party – please specify:

Please continue on next page.

B. General

11. With the EU pharma package the EU commission targets to inform patients about the key information of medicinal products. Are you aware of these plans?

☐ No

☐ Yes – if yes have you already started considerations/actions/projects?

☐ No – if no, why not?

☐ Yes – if yes, please specify:

12. The new "Guideline on Summary of Products Characteristics" as of September 2009 asks to summarise the key safety information in section "4.8 Undesirable effects" / sub-sections "a. Summary of the safety profile" and "c. Description of selected adverse reactions". Are you aware of this requirement to be implemented in May 2010?

☐ No

☐ Yes – if yes have you already started considerations/actions/projects?

☐ No – if no, why not?

☐ Yes – if yes, please specify

13. Your personal comments

This questionnaire will be part of my master thesis.

Please note that this questionnaire will be handled and evaluated anonymously. Your name and/or the name of your company will not be mentioned.

Thank you for your time and your support.

Annex 3: Definition of Key (Safety) Information in Attendee's Own Words – Compiled Table

Definition of Key (Safety) Information in Attendee's Own Words

General Definition of "Key (Safety) Information"

- The minimum of the information to be known on a product both on the pharmaceutical point of view, but also in terms of safety information/safety profile.
- Most important information for patient to decide if he/she can use the drug safely
- Important information which ensures the use of the product safely and appropriately
- Key information/key safety information are the specific details in the package leaflet which need to be fully understood by the patient in a way that he can assess the risks associated with taking the medicines in his hands. Consequently, the patient should be able handle the medicinal product appropriately to not expose himself to risks exceeding the ones which are outlined in the package leaflet.
- Information crucial for correct and safe use the medicinal product
- What the medicine product does, how it works and what side effects it may cause, and why doctor prescribes this medicine for me. I also want to know what I need to do to ensure safe and effective use of this medicine.
- Essential information necessary for the safe and efficient application and use of a medicinal product and for the identification of unwanted effects.
- Safety information that patients have to understand and how fast they can find this information in the PIL in regard to appropriate use of the product.
- The information that allows the user to take the medicinal product correctly and safely.
- Information which, if patients did not receive or understand, could cause a serious problem.
- The parts of information that are vital for effective and safe use of the medicinal product, both for patient and doctor/pharmacist
- Key safety information is all information that a patient needs to use safely and effectively a medicinal product.
- Key information is the most important information of the PL, the information that is crucial/minimum to have to use the medicinal product properly and without health risk.
- Key (safety) information is the least information that someone (doctor/patient) should know about when prescribing/taking this medicinal product.
- What is important for a patient to know before/during use
  What is important to know for an unexpected accident
- The information within the leaflet (determined by the content of the SmPC and any other useful information on the product/management of the disease) that is considered most key to the patient's understanding of how to use the product in a way that:
  1/ minimises any potential risk to their safety
  and
  2/ maximises the potential benefit they will receive from the product.
- Key information: Essential information that needs to be respected for an adequate use of the product (in terms of efficacy and/or safety)
  Key safety information: Information that is intended to prevent, inform or warn about risk of serious and/or long term and/or vital adverse reactions (would it be in case of normal use, misuse or overdose)
- Information that, if not understood correctly, would jeopardise the safety of the patient or his/her relevant intake of the drug
- To use the product in-label. Death related to drug, and overdose use
- Key safety information is what the consumer is most interested in for using the product correctly and which is important to be told to him for reasons of safety and compliance. This info needs to be found most easily and quickly within the whole product information available.
- Most important information without ignoring essential details regarding the safety of a medicinal product
- Information that is necessary for safe use

Definition of Key (Safety) Information in Attendee's Own Words

- Key (safety) information are those data that are mandatory for the patients to ensure proper and safe use of the medicinal product
- I define "key information/key safety information" as the information described in the PIL that needs definitely to be understood by the patient.
- Correct use of the medicinal product and information about the risks of the application of the medicinal product
- Important information for the patient on how to use the product and what to take care of
- The patient should understand all the necessary information on the medicine in order to follow his therapy in the better way.
- Provide the most important information without going too deep into details.
- Information necessary for the correct and safe usage of the medicinal product.
- Important information for the correct and safe use of the product written in a clear way and format that is understandable by any person that reads it independently of the schoolarity.
- Key information informs me on what is the product and what is the indication, how much, how and when/how long should I take it under which conditions should I not use this product which severe side effects can occur when I take it
- That information the patient needs to understand to use the medicinal product how he should (i.e. dosage) and when he needs consult a doctor (contraindication, adverse event….)
- Information which is essential for a safe application of the medicinal product, e.g. information regarding dosing, contraindications, warnings. If a patient does not fully understand such key information this cause a potential risk for him. He needs to understand the key safety information and needs to understand how to react on it.
- Information on how to take the medicinal product & any side effects.
- Any information on how to use the drug and when to stop using it.

General Definition including Examples / PL Sections

- Patients have to know how to use the product (posology), they should be informed about warnings, contraindications and possible side effects.
- Any information which defines the drug itself, its mode of action and the safety profile. For patients the section "contraindications" and interaction with other medicinal products and other forms of interaction
- The key safety information is the information which contains major details for all users and applicants - independent from level of knowledge. Such information as for example how to use, dosage, warnings, side effects, interactions,.. should be clear and reader friendly described.
- Any information that is of importance for the user to know before taking the drug, such as manner of administration/application, side effects, warnings, in-use stability, storage conditions, contraindication with other drugs, safety information regarding pregnancy and lactation etc.
  short, pregnant and understandable
  It is important for the user, that the information is given
- Information needed to assess the general safety profile of the product (e.g. possible side effects, interactions etc.)
  Information that is needed for the patient to assess whether the product may be used safely for the particular condition (disease)
  The patient information about what to do and whom to contact in case of any safety-related problems
  Information on how to use the product safely
- Information essential for a patient to understand why the physician has prescribed this product (indication), how to administer it (dosage, way of administration), which side effects may occur, which other factors should be known (warnings, contra-indications), how to store it.

Definition of Key (Safety) Information in Attendee's Own Words
• It is the minimum information for safe and effective use. Normally there a various patterns of information e.g. indication (tell-information), Warnings (tell-information to be considered by the physician), Precautions (tell-decide-do information), adverse reactions (tell-do information to be considered by the patient) …, When from each pattern (e.g. Adverse reaction) one statement (e.g. headache) is picked to address it in the questionnaire, you have the key (safety) information collected. I.e. you do not need to address each statement in one pattern, if one statement out the pattern is understood you can deduct from this statement to the others of the same pattern.
• Key safety information: the information a user needs to safely apply a medicinal product. This includes especially information regarding indication, contraindications and special warnings, dosage recommendations under consideration of special populations (age, pregnancy/lactation etc.), overdose, interactions, but also storage conditions and expiry date. I would consider key information important general information on the medicinal without direct relation to safe application, such as composition, manufacturer or marketing authorization holder.
• Indications/contraindications, warnings, special usage requirements/recommendations, side effects
• Name of product, indications and dosages, application information, potential side effects and interactions and their percentage values
• Key information = entire package leaflet except Marketing Authorisation Holder ff
• Indication, how much and how to take the drug/side effects, warnings and precautions
• Key information: indication, posology/dosing instructions Key safety information: contraindications, special warnings, side effects, overdose
• PIL section 2, 3 and 4 = key safety information
• The key information/key safety information of the PIL are the domains "area of use" (indication, contraindications, warnings, special patient groups), "adverse events" (side effects, interactions), "dosing" (dosage, application, overdosing, duration of usage), "handling" (expiration, storage).
• Indication - dosage - warning - side effects

Declaration

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

München, 01.07.2010

(Claudia Kristl)