Study on the Package Leaflets and the Summaries of Product Characteristics of Medicinal Products for Human use

PIL-S study

Liset van Dijk
Susana Patrício Monteiro
Marcia Vervloet
Jolanda de Bie
DK Theo Raynor

ISBN
DOI

Table of Contents

Executive summary 7
1. Introduction 13
1.1 SmPC and PIL: pillars of information 13
1.1.1 Summary of Product Characteristics 13
1.1.2 Patient Information Leaflet 14
1.1.3 Assessment report 14
1.2 Objectives 15
1.3 Work packages 15
1.3.1 WP 1: Identification of positive points and possible shortcomings o 15
1.3.2 WP 2: Identification of causes and consequences of shortcomings 16
1.3.3 WP3: Recommendations for improvement 16
Chapter 2 Legal context 17
2.1 Introduction 17
2.2 Directive 2001/83/EC and Regulation 726/2004 17
2.2.1 General 17
2.2.3 Directive 2001/83/EC and Regulation 726/2004 on the SmPC 18
2.2.4 Directive 2001/83/EC and Regulation 726/2004 on the Package Leaflet 20
2.3 Guidelines 23
2.3.1 Guideline on SmPC and on the packaging information 23
2.3.2 Guideline on the readability of the labelling and package leaflet 23
Chapter 3 Literature study 27
3.1 Methods 27
3.1.1 Search for scientific literature 27
3.1.2 Search for grey literature and previous literature reviews 29
3.2 Results scientific literature 29
3.2.1 Number of included studies 29
3.2.2 Comprehension and/or readability of the PIL 31
3.2.3 Design, lay-out and/or structure of the PIL 32
3.2.4 Completeness and/or consistency of information in the PIL 34
3.2.5 Evaluation of the SmPC 34
3.2.6 Medication information in general (among which the PIL) 35
3.3 Grey literature 37
3.4 Previous literature reviews 39
3.5 Summary 40
Chapter 4 Stakeholder survey - Patient Information Leaflet 43
4.1 Methods 43
4.1.1 Participants 43
4.1.2 Questionnaires 44
4.1.3 Measurements linked to research questions 44
4.2 Participants & their characteristics 46
4.2.1 Response 46
4.2.2 Characteristics of participants 47
4.3 Content and layout of PILs 51
4.3.1 Judgement on content and layout 51
4.3.2 Specific issues on content 54
4.3.3 Lay-out related issues 57
4.3.4 Digital alternatives for the PIL 58
4.4 Problems & consequences and positive points 59
4.4.1 Perceived problems & consequences 59
4.4.2 Positive points of the PILs 60
4.5 Regulatory issues 62
4.5.1 QRD-template 62
4.5.2 Regulation of OTCs 63
4.5.3 User testing 64

4.6 Solutions to further improve the PIL 64
4.6.1 Solutions mentioned by stakeholders 64
4.6.2 Trade-offs between potential solutions to improve the PIL 65
4.6.2 Sections to be included in the PIL 69
4.7 Summary main results 69
Chapter 5 Stakeholder survey -Summary of Product Characteristics 71
5.1 Methods and participants 71
5.2 Use, judgement of content & layout of SmPCs 72
5.2.1 When to consult the SmPC? 72
5.2.2 Judgement on content, layout and overall quality 72
5.2.3 Current content of the SmPC 74
5.2.4 Highlighting information in the SmPC 75
5.3 Perceived problems & consequences and positive points of the SmPC 75
5.3.1 Perceived problems & consequences of the SmPC 75
5.3.2 Positive points of the SmPC 76
5.4 Regulatory questions on the SmPC 76
5.5 Summary main results 79
6. Online discussion forum 81
6.1 Method 81
6.1.1 Participants 81
6.1.2 Method of online discussions 81
6.3 Results 82
6.3.1 Legislation and QRD 82
6.3.2 Length of the PIL 83
6.3.3 Font size and line spacing 85
6.3.4 Design & Content (in light of legislation & guidelines) 86
6.3.5 Comprehensibility-related problems 88
6.3.6 Risk and benefit information 89
6.3.7 How to communicate important information 90
6.3.8 Multilingual PILs 90
6.4 Summary of main results 90
Chapter 7 Discussion and conclusion 93
7.1 Main objective and assessment 93
7.2 Legal context 93
7.3 Patient information leaflet 95
7.3.1 Problems 95
7.3.2 Discussion on solutions 95
7.4 SmpC 98
7.5 Limitations of the study 98
7.6 Conclusions and recommendations 98
References 101
Appendix 1.A Main characteristics of relevant studies reporting positive points and potential problems with the PIL or SmPC (Chapter 3) 105
Appendix 1B List of excluded studies based on full text assessment 133
Appendix 2 Extra tables chapter 4 (open questions) 139

Executive summary

Background

The package information leaflet (PIL) and the summary of product characteristics (SmPC) form an intrinsic part of the authorisation process for medicinal products in the European Union. All medicinal products that are authorised by competent authorities of the individual Member States or by the European Commission (EC) are obliged to have completed and submitted both documents as an application to the European Medicines Agency (EMA) before marketing is authorised.

Assessment

The objective of this study is to provide the European Commission with:

1. An analysis of positive points and possible shortcomings of PILs and SmPC as a source of information about medicines for healthcare professionals and the public;
2. An analysis of the causes of identified shortcomings, and their (potential) consequences for the health of patients;
3. Recommendations to improve the SmPC and the PIL in order to increase their value for health care professionals and the general public, as well as their contribution to patient safety and the rational use of medicine.

The assessment included an extensive literature search, a European-wide stakeholder survey and an online discussion forum (see box, page 12). Before going into the conclusions of the assessment we summarise the legal context of the PIL and SmPC.

Summary of the legal context

Directive 2011/83/EC

Directive 2011/83/EC requires that all medicinal products authorised within the EU are obliged to have a PIL and a SmPC. This holds both for products that are authorised through a centralised procedure and for products that are authorised through a decentralised procedure. Article 11 of Directive 2011/83/EC describes the information that is required to be included in the SmPC. The PIL has to be drawn up in line with the SmPC and its requirements are laid down in article 59 of the same Directive. This last article mentions eight major subjects to be included in the PIL. Another requirement is the obligation for patient consultation to ensure that the leaflet is legible, clear and easy to use. The Directive also pays attention to the comprehensibility of the PIL by stating that the PIL should enable appropriate use. In general, package leaflets have to be available in the official language or languages of a Member State (article 63).

Guidelines

The following European guidelines are relevant for the Patient Information Leaflet or SmPC:

1. Guideline on Summary of Product Characteristics (September 2009) which explains for each section to be included in the SmPC what has to be addressed in that particular section;
2. Guideline on the packaging information of medical products for human use authorised by the Union (Final – version 14, July 2013) which has been prepared in order to describe how the provisions of Directive 2001/EC/83 apply in case of an authorisation granted by the Union (centralised marketing authorisation process);
3. Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, January 2009) of which the main purpose is "to provide guidance on how to ensure that the information on the labelling and package leaflet is accessible to and can be understood by those who receive it, so that they can use their medicine safely and appropriately". Additionally, the guideline includes guidance on how to consult target patient groups for the package leaflet.

QRD templates

The Quality Review of Documents group (QRD)[1] developed templates which provide the official wording to be used in the SmPC and PIL in accordance with Directive 2001/83/EC. With these templates, consistency across different medicinal products and across all Member States is aimed for.

User testing

For all marketing authorisations granted after 30 October 2005, the package leaflet has to be checked and information on patient consultation has to be included in the application dossier. One way to consult patients is through user-testing of the package leaflet. By such testing, problem areas in leaflet can be identified and improved accordingly. User testing only has to be done in one official language of the European Union (EU). Translation has to be undertaken using the process of 'faithful translation'.

Conclusions based upon the assessment

From the assessment through a literature study, a European wide stakeholder consultation and an online expert discussion six main conclusions were derived.

Conclusion 1: Room for improvement of PIL more so than for SmPC

Patients' comprehension of the PIL and its readability can be improved. The language used is often too complex and the design and lay-out are not always user-friendly. The elderly and those with low literacy skills are disadvantaged, but generally these problems hold for all patient groups. Especially information about interactions, contraindications, dosage instructions and side effects is complex and there is a lack of benefit information to be found in the PIL in order for patients to make a balanced

[1] The Working Group on Quality Review of Documents (QRD) provides assistance to the Agency's scientific committees and to companies on linguistic aspects of the product information for medicines (summaries of product characteristics, labelling and package leaflets).

informed decision. Small font size, narrow line spacing and the length of the PIL are lay-out related problems most frequently noted. Consequences of these problems are that readers may give up reading the PIL and miss important information. This may lead to inappropriate actions such as non-adherence to their medication. Additionally, patients may get confused or worried for example because of the extensive list of side-effects.

For the SmPC less problems are signalled. Although the information is not always complete and sometimes outdated representatives of Health Care Professionals (HCPs) in our study judge the quality of the SmPC as reasonable and value most of the current topics addressed in the SmPC as being important. Information on issues related to children is one of the few items that were noted as missing. However, two recent studies in Germany and the United Kingdom (UK) showed that SmPCs in practice are not seen as valuable nor often used by physicians. As such, improvements can be made especially with regard to the readability of the SmPC. Research showed that simpler language and a more clear structure in the SmPC were helpful for HCPs in finding and understanding information. Also a key information section was valued.

Conclusion 2: Adapt guidelines and QRD-template to enhance readability of patient information leaflets

In order to improve the current situation adaptation of guidelines is easier than adaptation of legislation. Most of the problems mentioned in the assessment can be handled by improving guidelines. The current guidelines are considered not to be clear in several respects, for example with regard to the recommendations for font sizes and line spacing. Another issue is that the guidelines are considered too restrictive in some respects and that more flexibility is needed as medicines and contexts may differ. This also holds for the QRD, where information not relevant to the patient could be removed such as information on all available pack sizes and doses, to release valuable space to make improvements in content and layout. A step forward in this regard, taken while this research was taking place, was the removal of the requirement for information on all Marketing Authorisation Holders. The guidelines could include more detail on the principles of good information design in which content and lay-out are jointly considered. The stakeholder consultation showed that PILs that received higher scores on lay-out and design-related issues also received higher scores for content-related issues.

Conclusion 3: Strengthen patient input in developing and testing of PILs

As of October 30, 2005 user testing of PILs is required for new medicines. PILs developed after this requirement has been introduced are considered to be more clear and user friendly, but still improvements can be made. Stakeholders in the assessment asked for strengthening the input from the patient perspective. This could also help in getting more sense on how to present risk-benefit information for a particular drug as throughout the assessment it was clear that there is no consensus on how to best present (the balance between) adverse effects and benefit information. User testing should be an iterative process in which a first version of the leaflet is

tested, the leaflet is adapted accordingly to the suggestions, new patients test the leaflet again etc. Additionally, further improvements in the process of patient consultation can be achieved. A first example is that user testing in only one language is required. Yet, it is known that in translating the original tested PIL, lay language is sometimes translated back to more formal language. Therefore, back and forth translation could be required and/or testing of the PIL in more than one language. Another example is that patient consultation is done during the process of market authorisation. Sometimes last minute changes in the information are required by the authorising body which are not then subject to user testing.

Conclusion 4: Best practice should be promoted

Guidelines and the QRD template provide instructions and help in how to compose a PIL and SmPC. However, they do not provide good examples. Good, user-tested examples could be promoted more by EMA and national regulatory agencies, making it easier for the industry to follow the good examples. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has put this into practice. Information technology makes sharing best practice on a large scale possible. Hereby, it is recommended not only to show the end result of such good example but also to share the information development process of good examples, for example how the input of patients was organised and included.

Conclusion 5: Development of an integrated strategy for (electronic) PIL-formats

The PIL does not stand alone. To reach the goal that patients act appropriately there needs to be a combination of information provided by the health care professional which is supported by the PIL accordingly. As of now the PIL is not designed to be part of such integral process on patient information with the exception that it tells patients when to consult a doctor. This may require more flexibility in the content of the PILs. Patients have, for example, a different need for information when they start a treatment compared to when they are "experienced" users. More flexibility is difficult to reach in the current situation with the requirement of a paper PIL within the pill box. Electronic formats bring new opportunities for flexibility, while leaving the paper PIL as it is. Currently, not every EU-citizen is prepared for the whole range of opportunities provided by new information technologies. In 2011, 15% of EU citizens had never used the internet, but large variation existed across between Member States. Yet, as more and more Europeans gain access, the potential for the use of electronic formats to provide the information alongside the paper PIL in an optimal way to individual EU-citizens should be considered.

Conclusion 6: Multilingual PILs can benefit from electronic formats

In general, countries with more than one official language require multilingual PILs. As it needs to contain the same information in all languages it can become large, font sizes become small and line spacing narrow. Those problems mentioned for all types of PILs are worse for the multilingual PIL. So far, the principle of faithful translation is used in the EU and user testing is only required in one EU-language. Therefore, there is the risk that translated versions of PILs are less suited for lay people than the original version. This problem is however not unique to multilingual PILs (see also conclusion 3). What is unique for multilingual PILs is that they are only user-tested on their content, but not on lay-out and design. Because of their increased content, design and lay-out are particularly important aspects of multilingual PILs.

Electronic formats may play an important role in the future especially in multilingual countries, for example by providing a combination of paper and electronic formats where the most relevant information is included in the paper format and the rest can be found in electronic format. Electronic media would also allow people to choose from all languages available. Until wider access is realised other solutions could be sought for. An example is to use a booklet format with tabs for different languages.

Recommendations to the European Commission

Based upon the above the following recommendations are made:

1. Focus on improvement of the PIL rather than on the SmPC.
2. Consider reformulating the guidelines so that they include more principles of good information design and consider allowing for more flexibility in the information recommended in the QRD template between medicines as long as legislation allows it. Include guidelines on translation that go beyond the principle of faithful translation, in order that the lay language introduced through user testing in the original language is not lost during translation.
3. Further strengthen the input from patients during the development process for example by requiring to:
   - make the user testing process more iterative;
   - user test changes in information required by regulators after the initial user testing
4. Make best practice examples of aspects of leaflet design (anonymised) available for pharmaceutical companies and include not only the end product but also information on the process of development where possible.
5. Examine the potential to use electronic media in the (near) future as an increasing number of EU-citizens gets access to these media:
   a) Explore opportunities these media offer for optimizing the PIL in terms of flexibility of information provided and design.
   b) In doing so, explore and research the opportunities for the PIL to be part of the care process rather than a stand-alone source of information.
   c) Consider how mechanisms to alert patients taking long-term medicines to changes in the PIL could be developed through electronic media.
6. Consider those countries with more than one official language in the electronic media strategy.

Methods used in the assessment

Existing evidence on PIL and SmPC in the literature
Collection of existing evidence on the PIL and SmPC by an extensive literature search in the following electronic databases: PubMed, Embase, Sociological Abstracts and Communication and Mass Media Complete, Digital Repository Infrastructure Vision for European Research (DRIVER) and Scirus. This resulted in 61 articles in international journals, two major reports and three reviews of the literature.

European wide stakeholder consultation
The following stakeholder groups were consulted twice through an online structured questionnaire: Patient and consumer organizations, health care provider organizations, pharmaceutical industry, regulatory officers and communication experts. Participants represented a wide variety of countries in the EU. Participants answered a wide variety of question including questions on six specific patient information leaflets and summaries of product characteristics.

Online discussion forum
An online discussion forum was opened involving two representatives of European level patient organizations, three representatives of health care professional organizations, four regulatory officers, seven experts on communication in the PIL and five representatives of the pharmaceutical industry. Representatives of the pharmaceutical industry had a separate forum for discussion because they may have different interests.

Introduction

1.1 SmPC and PIL: pillars of information

Many European citizens use medicinal products on a regular or long-term basis and their number will be increasing because of the aging of the population. Information on why and how to use medication as well as on the characteristics of medication is crucial to patients and health care professionals. Important pillars of information on medicinal products across Europe are the:

- **Patient Information Leaflets** (PILs) for patients, referred to in EU legislation and guidance as Package Leaflets (PLs) and
- **Summaries of Product Characteristics** (SmPC) for professionals (outside Europe the equivalent documents are described as the Product Information or PI).

All medicinal products that are authorised by competent authorities of the Member States (in accordance with *Directive 2001/83/EC*)[2] or by the European Commission (in accordance with *Regulation No726/2004*) are obliged to have both a PL (Package Leaflet – referred to in this document as a patient information leaflet (PIL)) and a summary of product characteristics (SmPC). Both documents must be completed and submitted as an application to the EMA/competent authority before marketing is authorised. As such, the SmPC and the PIL form an intrinsic part of the authorisation process.

1.1.1 Summary of Product Characteristics

The SmPC is the definitive description of the product, both in terms of its properties (chemical, pharmacological etc.) and how the product has to be used for a specific treatment. It sets out "the agreed position of the medicinal product as distilled during the course of the assessment process". The SmPC can be consulted directly by health care professionals, but is also often incorporated in other information sources aimed at health care professionals, such as national information databases. The European Union provides a guideline for companies that apply for authorisation of a medicine on how to compose this document.3 Once the product is approved the SmPC cannot be changed, except when the competent authority approves of such change. Scientific studies show some problems with the SmPC. Bergk (2005), for example, found that SmPCs provided medicinal products interaction information for only 33% of the 579 evaluated combinations for which evidence was found in the literature (1). Additionally, Wall et al. (2009) showed that significant discrepancies exist between poisoning management advice contained in SmPC documents and the primary clinical toxicology database in the UK (2). Arguello & Fernandez-Llimos (2007) concluded that the clinical pharmacology information found in SmPCs in the European Union is insufficient and that improved access to and regular review of SmPCs might substantially improve the access and quality of clinical pharmacology and other prescribing information (3). Moreover, SmPCs can differ between countries, which may cause problems. Ursino et al (2011) found that warnings in SmPCs on gastrointestinal products were more detailed in SmPCs from the US and the UK compared to those from Italy (4). They concluded that the frequent lack of details on safety issues –

[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20091005:EN:PDF
[3] http://ec.europa.eu/health/files/eudralex/vol-2/c/SmPCguidrev1-oct2005_en.pdf

which was more prevalent in Italy – in the SmPCs makes it difficult for health professionals to provide relevant advice.

1.1.2 Patient Information Leaflet

The PIL is an important source of information for patients as it is the only mandatory piece of information about a medicine for patients. Delivery to the patient is assumed to be guaranteed, because of its presence inside the medicine pack. It is based upon the information in the SmPC. The PIL should include a set of comprehensible information to inform patients how to use the product safely and appropriately. In addition, marketing authorisation holders should ensure that PILs are made available on request from patients' organisations in formats appropriate for the blind and partially-sighted (*Directive 2001/83/EC, article 56a*). The information on the PIL should reflect the results of consultations with the target group to ensure that it is legible, clear and easy to use (*Directive 2001/83/EC, article 59 (3)*) and the results of these assessments should be provided along with the draft package leaflet submitted to the competent authority upon marketing authorisation application (*Directive 2001/83/EC, article 61*). The leaflet should be available in all official languages of the Member State where the product is marketed (although there are exceptions)[4] and the language used should be clear and understandable (*Directive 2001/83/EC, article 63*). The 2001 Directive was amended several times (see chapter 2 for more extensive information on the EU legislation).

While considerable efforts have been made at EU-level to improve the information provided in the PIL, there has been considerable criticism. This criticism includes that the PILs are hard to read and understand (5). Several studies on PILs confirm this criticism (6;7). Readers encounter problems in finding the right information. Dixon-Woods (2001) argues that the reason for PILs not to be easily understood, may be that the focus is too much on the concept of readability (8). This arises from the biomedical perspective of the PIL being a source of patient education (with a passive role for the patient) rather than a source for patient empowerment where the patient has an active role and values patients' rationality, competence, resourcefulness and reflexivity (8). For communication to be effective the information should be noticed, read, understood, believed and remembered. When this goal is not reached this may have negative consequences, such as non-adherence to medication because of misinterpretation of the risk for side-effects. Vulnerable groups are especially at risk for these failures, as it is very hard to fulfil all criteria for effective (written) communication for these groups. It should be noted that – as of 2005, the requirement for consultations with target patient groups (described above) came into force for new medicines. Most studies which criticise the PILs relate to leaflets which have not been through such consultations.

1.1.3 Assessment report

Given the problems observed with both the SmPC and the PIL, directive 2010/84/EU called upon the European Commission to present an assessment report to the European Parliament and the Council that discusses the readability and comprehensibility of both the PIL and the SmPC as well as their value to health

4 Article 63.3 reads: when the product is not intended to be delivered directly to the patient, the competent authorities may grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and that the leaflet must be in the official language or languages of the Member State in which the product is placed on the market. Article 63(1) states: in case of certain orphan medicinal products […] the particulars listed in Article 54 may, on reasoned request, appear in only one of the official languages of the Community".

professionals and consumers (the general public). NIVEL, Netherlands institute for health services research, prepared this assessment report together with the University of Leeds. The results of the study should contribute to one of the strategic objectives in the Commission White Paper *"Together for Health: A Strategic Approach for the EU 2008-2013"* (2007), namely the objective of "fostering good health in an ageing Europe".

1.2 Objectives

The objective of this study was to provide the European Commission with:

- an assessment of the readability and comprehensibility of the package information leaflets (PIL) and the summaries of product characteristics (SmPC) as a source of information on prescription and non-prescription medicines for patients and health care professionals
- an assessment of the causes and (potential) consequences of identified shortcomings and
- recommendations for improvement of patient leaflets and summaries of product characteristics of prescription and non-prescription medicines based on this assessment.

The study paid attention to older persons, those with low literacy, the rational use of medicines and patient safety in the readability, layout and content of PILs and SmPCs. The legal context of EU legislation and other relevant EU level policy documents (including guidelines) was taken into consideration. Only EU-level legislation and guidelines were concerned.

1.3 Work packages

To create the assessment described in section 1.2 the following steps were taken:

- An analysis of positive points and possible shortcomings of PILs and SmPC as a source of information about medicine for healthcare professionals and the public. (Work package 1);
- An analysis of the causes of identified shortcomings, and their (potential) consequences for the health of patients. (Work package 2);
- Formulating recommendations to improve the SmPC and the PIL in order to increase their value for health care professionals and the general public, as well as their contribution to patient safety and the rational use of medicine. (Work package 3).

The three work packages each had their own focus.

1.3.1 WP 1: Identification of positive points and possible shortcomings of PILs and SmPCs, as regards the value as a source of information.

WP1 focused on the identification of positive points and possible shortcomings of both PILs and SmPCs for prescription medicines. The following questions were answered in this WP:

WP1.1 *To what extend does the current content, design and layout of different PILs allow users to find and comprehend the necessary information about their medicine and enhances their adherence to their treatment?*

WP1.2 *To what extend does the current content design and layout of SmPC provide health care professionals with necessary information how a medicine should be used?*

In answering these questions, we paid special attention to the elderly, as well as on the rational use of medicines and patient safety.

1.3.2 WP 2: Identification of causes and consequences of shortcomings of PIL and SmPC

In WP2 the shortcomings detected in the PILs and the SmPCs were further analysed. The following questions were answered in this WP:

WP 2.1 Which causes can be identified for shortcomings in PILs and SmPCs?

WP2.2 To what extend can the failure to understand the PIL or the information from the SmPC (including sources based upon the SmPC) lead to prescription or medication errors, which may result in non-rational use of medicine or suboptimal patient safety?

Attention was paid to the consequences for vulnerable populations, such as older persons and those with low literacy.

1.3.3 WP3: Recommendations for improvement

WP 3 focused on what recommendations can be made to improve the PIL and SmPC. The following question was answered:

WP 3.1 What recommendations can be made for the improvement of the SmPC and the PIL (with regard to content, design and layout) in order to increase their value for the healthcare professionals and the general public as well as with respect to their contribution to the rational use of medicines and patient safety?

As in the other work packages, attention was paid to recommendations concerning consequences for vulnerable populations, such as older persons and those with low literacy. Recommendations were made taking into account the legal context of EU legislation and other relevant EU level policy documents.

Chapter 2 Legal context

2.1 Introduction

All medicinal products that are authorised by competent authorities of the European Union Member States (in accordance with Directive 2001/83/EC)[5] or by the European Commission (in accordance with Regulation No726/2004) are obliged to have both a package information leaflet (PIL) and a summary of product characteristics (SmPC). The 2001 Directive was amended several times. Additionally, several guidelines were developed at the EU-level, QRD-templates were introduced as well as user testing. This chapter describes the relevant legal framework regarding PILs and SmPCs within the context of the European Union from 2001 onwards.

2.2 Directive 2001/83/EC and Regulation 726/2004

2.2.1 General

Directive 2001/83/EC of the European Parliament and of the Council relates to medical products for human use. Directive 2001/83/EC was amended several times (http://ec.europa.eu/health/documents/eudralex/vol-1/). With regard to the PIL and the SmPC a major change took place in 2004 when Directive 2004/27/EC amended Directive 2001/83/EC (Official Journal L 136, 30/4/2004 p. 34 - 57). With this amendment the articles 11 – on required information in the SmPC – and 59 – on required information in the PIL were included in its current forms. The last consolidated version of Directive 2001/83/ (http://ec.europa.eu/health/documents/eudralex/vol-1/) EC stems from November 16, 2012. This version was used for the description provided below.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 describes Community procedures for the authorisation and supervision of medicinal products for human and veterinary use.[6] The last consolidated version of Regulation 726/2004 stems from June 5 2013 (http://ec.europa.eu/health/documents/eudralex/vol-1/). This version is used for this chapter.

[5] http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20091005:EN:PDF

[6] Additionally, the Regulation describes the establishment of EMA.

2.2.3 Directive 2001/83/EC and Regulation 726/2004 on the Summary of Product Characteristics

The recitals of Directive 2011/83/EC reads that: "*(52): Persons qualified to prescribe or supply medicinal products must have access to a neutral, objective source of information about products available on the market. Whereas it is nevertheless for the Member States to take all measures necessary to this end, in the light of their own particular situation.*" The Summary of Product Characteristics is meant to provide professionals with this information.

In Title III of the Directive, Placing on the Market, it says that in order to obtain an authorisation for a medicinal product on the market a summary of product characteristics (SmPC) should be provided (article 8j). Also in Annex 1 of the Directive it reads that a proposed SmPC should be part of the marketing authorisation dossier (section 1.3.1). The SmPC has to be in accordance with article 11 of the Directive (see Box 2.1). Authorisation will be refused in case the SmPC is incorrect (article 12 of the regulation). According to article 57.1.b of Regulation 726/2004 the European Medicines Agency has as one of its tasks to transmit – on request – and making publicly available SmPC for medicinal products. Additionally, article 57.2 states that EMA should include SmPCs in a database on medicinal products (as described in article 57.1.l).

Since the establishment of the European Medicines Agency (EMA) in 1995 there are two ways for pharmaceutical companies to obtain authorisation for their products (9;10): through a decentralised procedure or through a centralised procedure. Centralised procedures grant authorisation through a Commission decision, which makes the decision valid in all Member States. In a decentralised procedure, Member States have the possibility to follow the principle of mutual recognition (9). This means that applications go to the 'Reference Member State', which is "the market where the company wishes to first launch its product, and the agency facilitates recognition of marketing authorisation by other 'Concerned Member States'" (10). When the market authorisation is issued decentralised, the national competent authorities of the reference Member State have to make the authorisation publicly available along with the SmPC (article 21.3).

Box 2.1 Article 11 of Directive 2001/83/EC on information required in the SmPC

The summary of the product characteristics shall contain, in the order indicated below, the following information:

1. name of the medicinal product followed by the strength and the pharmaceutical form.
2. qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.
3. pharmaceutical form.
4. clinical particulars:
   - 4.1. therapeutic indications,
   - 4.2. posology and method of administration for adults and, where necessary for children,
   - 4.3. contra-indications,
   - 4.4. special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,
   - 4.5. interaction with other medicinal products and other forms of interactions,
   - 4.6. use during pregnancy and lactation,
   - 4.7. effects on ability to drive and to use machines,
   - 4.8. undesirable effects,
   - 4.9. overdose (symptoms, emergency procedures, antidotes).
5. pharmacological properties:
   - 5.1. pharmacodynamic properties,
   - 5.2. pharmacokinetic properties,
   - 5.3. preclinical safety data.
6. pharmaceutical particulars:
   - 6.1. list of excipients,
   - 6.2. major incompatibilities,
   - 6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,
   - 6.4. special precautions for storage,
   - 6.5. nature and contents of container,
   - 6.6. special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate.
7. marketing authorisation holder.
8. marketing authorisation number(s).
9. date of the first authorisation or renewal of the authorisation.
10. date of revision of the text.
11. for radiopharmaceuticals, full details of internal radiation dosimetry.
12. for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

For authorisations under Article 10, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included.

For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary of product characteristics shall include the statement: 'This medicinal product is subject to additional monitoring'. This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system referred to in Article 107a(1). Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of Article 107a(1).

2.2.4 Directive 2001/83/EC and Regulation 726/2004 on the Package Leaflet

The recitals of Directive 2011/83/EC reads that: *"(39): Rules should be laid down as to how labelling and package leaflets are to be presented".* A package leaflet is defined as: a leaflet containing information for the user which accompanies the medicinal product (Article 1, point 26 of Directive 2001/83/EC).

Marketing authorisation

In Title III of the Directive, Placing on the Market, it says that in order to obtain an authorisation to place a medicinal product on the market a package leaflet should be provided (article 8j). This requirement is also laid down in Annex 1 of the Directive which reads that a proposed package leaflet should be part of the marketing authorisation dossier (section 1.3.2.). The package leaflet has to be in accordance with article 59 of the Directive (see below). The process is similar compared to that of the SmPC as both documents are an obligatory part of the authorisation. Authorisation will be refused in case the leaflet is not in line with this title (article 12 of the regulation). According to article 57.1.b of Regulation 726/2004 the European Medicines Agency has as one of its tasks to transmit – on request – and making publicly available package leaflets for medicinal products. Additionally, article 57.2 states that EMA should include package leaflets in a database on medicinal products (as described in article 57.1.l).

Requirements for package leaflets

Title V of Directive 2001/83, Labelling and Package Leaflet, is partly devoted to the requirements for package leaflets. The package leaflet has to be drawn up in accordance with the SmPC. The inclusion of patient leaflets is obligatory unless all the information required by articles 59 and 92 is directly conveyed on the outer packaging or on the immediate packaging (article 58). The information that is required in the package leaflet (article 59) is described in Box 2.2. If the package leaflet does not comply with these requirements or is not in accordance with the particulars listed in the Summary of Product Characteristics the competent authority has to refuse to grant the marketing authorisation (article 61.2). All proposed changes to the leaflet covered by title V of Directive 2001/83/EC and not connected to the SmPC have to be submitted to the competent authorities for authorising marketing (article 61.3).

Comprehensibility for patients

Article 63 of Directive 2001/83/EC states that package leaflets have to be provided in the official language or languages of the Member State where the medicinal product is placed in the market. For countries with more than one official language this results in multilingual leaflets for most medicines. Article 62 states that package leaflets may include symbols and pictograms in order to clarify information for patients. Article 56.a states that marketing authorisation holders have to ensure that the package information leaflet is made available in request from patient organizations for the blind and partially-sighted.

Box 2.2 Article 59 of Directive 2001/83/EC on information required in the package leaflet

1. The package leaflet shall be drawn up in accordance with the summary of product characteristics; it shall include; in the following order:

a. for the identification of the medicinal product:
   i. the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the product contains only one active substance and if its name is an invented name;
   ii. the pharmaco therapeutic group or type of activity in terms easily comprehensible for the patient;
b. the therapeutic indications;
c. a list of information which is necessary before the medicinal product is taken:
   i. contra-indications;
   ii. appropriate precautions for use;
   iii. forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;
   iv. special warnings;
d. the necessary and usual instructions for proper use, and in particular:
   i. the dosage,
   ii. the method and, if necessary, route of administration;
   iii. the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;
   iv. and, as appropriate, depending on the nature of the product:
   v. the duration of treatment, where it should be limited;
   vi. the action to be taken in case of an overdose (such as symptoms, emergency procedures);
   vii. what to do when one or more doses have not been taken;
   viii. indication, if necessary, of the risk of withdrawal effects;
   ix. a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product;
e. a description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case;
f. a reference to the expiry date indicated on the label, with:
   i. a warning against using the product after that date;
   ii. where appropriate, special storage precautions;
   iii. if necessary, a warning concerning certain visible signs of deterioration;
   iv. the full qualitative composition (in active substances and excipients) and the quantitative composition in active substances, using common names, for each presentation of the medicinal product;

v. for each presentation of the product, the pharmaceutical form and content in weight, volume or units of dosage;
vi. the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;
vii. the name and address of the manufacturer;

g. where the medicinal product is authorised in accordance with Articles 28 to 39 under different names in the Member States concerned, a list of the names authorised in each Member State;
h. the date on which the package leaflet was last revised.

For medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included '*This medicinal product is subject to additional monitoring'.* This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a(1), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Article 107a(1).

2. The list set out in point (c) of paragraph 1 shall:
a. take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions);
b. mention, if appropriate, possible effects on the ability to drive vehicles or to operate machinery;
c. list those excipients knowledge of which is important for the safe and effective use of the medicinal product and which are included in the detailed guidance published pursuant to Article 65.

2.3 Guidelines

In article 65 of the Directive it says that (in consultation with Member States and parties concerned) the Commission shall draw up and publish more detailed guidance concerning in particular:

a. the wording of certain special warnings for certain categories of medicinal products;
b. the particular information needs relating to non-prescription medicinal products;
c. the legibility of particulars on the labelling and package leaflet;
d. the methods for the identification and authentication of medicinal products;
e. the list of excipients which must feature on the labelling of medicinal products and the way in which these excipients must be indicated;
f. harmonised provisions for the implementation of Article 57.

The following European guidelines are relevant for the Patient Information Leaflet or SmPC:

1. A guideline on Summary of Product Characteristics (September 2009)[7];
2. Guideline on the packaging information of medical products for human use authorised by the community (Final – version 14, July 13)[8];
3. Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, January 2009)[9].

2.3.1 Guideline on SmPC and on the packaging information

The guideline on Summary of Product Characteristics (SmPC) provides advice on the principles of presenting information in the SmPC. It follows article 11 of Directive 2001/83/EC. Whereas the guideline explains for each section to be included in the SmPC the information that has to be addressed in that particular section, more practical advice can be found in the templates of the Quality Review of Documents group (QRD). The QRD provides the official wording to be used in the SmPC and PIL in accordance with Directive 2001/83/EC. With the QRD templates consistency across different medicinal products and across all Member States is aimed for. The templates define standard headings, standard statements and terms and the format and layout to be used.

The guideline on the packaging information of medical products for human use has been prepared in order to describe how the provisions of Directive 2011/EC/83 apply in case of an authorisation to granted by the Community (centralised marketing authorisation process). Section B of this guideline refers to package leaflets. The Community authorisation of a medicinal product includes the text of the leaflet. This text should be the same throughout the Community and should be available in the official language(s) of the Member State where the medicine is issued. The package leaflet in a Member State may contain additional information, of educational nature if compatible with the SmPC but which is not of promotional nature. In case a change of the package leaflet is proposed which is not in line with the SmPC the marketing authorisation holder should notify the competent authority, which would be EMA in case of centralised authorisation.

2.3.2 Guideline on the readability of the labelling and package leaflet

January 12 2009, the European Commission published the guideline on the readability of the labelling and package leaflet of medicinal products for human use. This

[7] ec.europa.eu/health/.../smpc_guideline_rev2_en.pdf
[8] http://ec.europa.eu/health/files/eudralex/vol-2/c/bluebox_06_2013_en.pdf
[9] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

guideline became effective on June 12, 2009. The guideline is in line with EU legislation (Directive 2001/EC/83). The main purpose of this guideline is "to provide guidance on how to ensure that the information on the labelling and package leaflet is accessible to and can be understood by those who receive it, so that they can use their medicine safely and appropriately" (p.6 of the guideline). The guideline is meant to support applicants and marketing authorisations holders in preparing the package leaflet and advises on the presentation of the content of package leaflet (required in accordance with Title V of the Directive) and on the design and layout concepts which will aid the production of quality information. Additionally, the guideline includes guidance on how to consult target patient groups for the package leaflet. It also includes information on how to make the package leaflet available in formats suitable for the blind and partially-sighted patients. Finally, the guideline includes an example on how to test the package leaflet.

Chapter 1 of the guideline starts with recommendations for the package leaflet and states that it should be designed and worded in such a way that a maximum number of people who can use the information benefits from it. Elements for which recommendations are provided in this chapter are listed in Box 2.3 along with examples of the recommendations. Chapter 1 also provides links to templates which include all the particulars which must appear in the package leaflet according to Directive 2001/83/EC. These QRD-templates are available in all official languages in the EU.

Box 2.3 Topics on which the guideline on the readability of the labelling and package leaflet of medicinal products for human use provides recommendations – including examples

1. Type size and font of the letter

An example of a recommendation in this section is that a type size of 9 points (as measured in Times New Roman) is considered as a minimum for the leaflet's text. Another example is that capitals should not be used widespread and that italics and underlining should be avoided.

2. Design and layout of the information

Examples of recommendations in this section include that the line spacing between one line and the next should preferably be at least 1.5 times the space between words on a line. Also contrast between text and background is important.

3. Headings

As heading are important they should stand out for example by choosing a bold type face or a different colour. Another recommendation is to be careful with the use of multiple levels of headings.

4. Print colour

The recommendations in this section refer for example to the relationship between colours where a general rule for package leaflets is that dark text should be printed on a light background.

5. Syntax

Here the guideline recommends to use simple words and few syllables and to avoid long sentences. The use of bullet point is recommended instead of long paragraphs.

6. Style

An active writing style is recommended and in case patients need to take action, reasons for doing so should be provided. Medical terms should be explained in such way that patients can understand them.

7. Paper

The guidelines recommends that the paper should be sufficiently thick to reduce transparency. The use of glossy paper is discouraged as it reflects light making reading more difficult.

8. Use of symbols and pictograms

According to the guideline symbols and pictograms can be used in case the symbol is clear and the size of the graphic makes it easily legible. They should, however, not replace the actual text in the leaflet. In case of doubt of the meaning of the pictogram its use is considered inappropriate.

9. Additional information

This information refers among other things to the fact that there should be a different leaflet for each strength and form of a medicinal product.

Chapter 2 of the guideline includes specific recommendations for blind and partially sighted patients. Most of the recommendations refer to the package itself, with the exception of section 6, where it is stated that "on request from patients' organisations the package leaflet should be provided for partially-sighted people in a suitable print, taking into consideration all aspects determining the readability" (p. 18). For blind persons it is recommended to provide the text in a format perceptible by hearing. In Chapter 3 consultation with target patient groups for the package leaflet is discussed.

User testing

For all marketing authorisations granted after 30 October 2005, the package leaflet has to be checked and information on patient consultation has to be included in the application dossier. The reason for this consultation is to ensure that it the leaflet is legible, clear and easy to use.
One way to consult patients is through user-testing of the package leaflet. User testing means "to test the readability of a specimen with a group of selected test subjects. It is a development tool which is flexible and aims to identify whether or not the information as presented, conveys the correct messages to those who read it." By testing, problem areas in a leaflet can be identified and improved accordingly. When user testing, the use of a full mock-up of the leaflet in the colours and style and on the paper as used for the leaflet in the marketed pack is required also for multilingual leaflets. Other methods than user testing have to be justified by the applicant.

In the following situations a user consultation is always required:
- First authorisation of a medicinal product with a new active substance,
- Medicinal products which have undergone a change in legal status,
- Medicinal products with a new presentation,
- Medicinal products with particular critical safety issues.

In case similar package leaflets are already tested, this evidence may be used where appropriate. Examples of such situations include extensions for the same route of administration, when the same safety issues are identified or when it is a product from the same class of medicinal product.

User testing only has to be done in one official language of the EU. In drafting the original leaflet, every effort has to be made to ensure that it can be translated to the various other national languages across the EU. This translation has to be undertaken using the process of 'faithful translation'. Yet, such faithful translation has been shown to be vulnerable as it can lead to many of the improvements resulting from the testing being lost, as the translators change it back into official-style language (11).

Chapter 3 Literature study

This chapter presents the literature search that has been conducted to provide an overview of what is already known in the literature about positive points and potential problems with the PIL and SmPC, looking both at issues regarding content and issues regarding design and lay-out. The first section describes the methodology used for the literature study. The results are presented in section 3.2. The last section provides a brief summary of the findings and the conclusions that can be drawn from the literature study. An extensive table summarizing all studies can be found in Appendix 1.

3.1 Methods

3.1.1 Search for scientific literature

Search strategy

A comprehensive literature search was conducted in the electronic database PubMed with the following search string:
("drug" [tiab] OR "Medication" [tiab] OR "medicinal product" [tiab] OR "prescriptions" [MeSH] OR "prescription drugs" [tiab] OR "self medication" [MeSH] OR "pharmaceutical preparations" [MeSH] OR "over the counter medication" [tiab] OR "OTC medication" [tiab]) AND ("packaging" [tiab] OR "package insert" [tiab] OR "package inserts" [tiab] OR "labelling" [tiab] OR "labeling" [tiab] OR "package leaflet" [tiab] OR "package leaflets" [tiab] OR "patient information leaflet" [tiab] OR "patient information leaflets" [tiab] OR "drug information leaflet" [tiab] OR "drug information leaflets" [tiab] OR "medication information" [tiab] OR "Consumer Health Information" [MeSH]) NOT "DNA" [tiab]
The following restrictions were applied: publication date from 2000, involving humans

This search was conducted December 13th, 2011, and updated in March 2013. The electronic search was supplemented by manual searching of reference lists of relevant articles ("snowball method") and the researchers' personal files.[10]

For the related PIL-s BOX study[11], we also conducted a literature search to identify existing evidence on the inclusion of a summary information section in the PIL and SmPC.[12] This search yielded possible relevant studies for this project as well . Therefore, we used the search for the PIL-s BOX project as an addition for the current project. For the PIL-s BOX study, a comprehensive literature search was conducted in the databases of PubMed, Embase, Sociological Abstracts and Communication and Mass Media Complete. The search string used for PubMed was:
(("drug" [tiab] OR "drugs" [tiab] OR "medication" [tiab] OR "medicinal product" [tiab] OR "prescription drugs" [MeSH] OR "nonprescription drugs" [MeSH] OR "self medication" [MeSH] OR "OTC" [tiab] OR "over the counter" [tiab] OR "innovative drugs" [tiab] OR "new medication" [tiab]) AND ("drug packaging" [MeSH] OR "packaging" [tiab] OR "drug labeling" [MeSH] OR "labeling" [tiab] OR "labelling" [tiab] OR "package insert" [tiab] OR "package inserts" [tiab] OR "package leaflet" [tiab] OR

[10] From here onwards referred to as snowballing method.
[11] Van Dijk L, Vervloet M, Montiero SP, Van der Burgt S, Raynor DK. The feasibility and the value added of a possible "summary information box" to be included in the patient information leaflets and the summaries of product characteristics of medicinal products for human use. 2014
[12] This study was performed by NIVEL and the University of Leeds as well and addressed the potential introduction of a key information section in the PIL and SmPC.

"package leaflets" [tiab] OR "information leaflet" [tiab] OR "information leaflets" [tiab] OR "patient information" [tiab] OR "summary product characteristics" [tiab])) NOT "DNA" [tiab] NOT "DNA" [MeSH]
The following restrictions were applied: publication date from 1995, involving humans

This search string was adapted for the other databases. PubMed was last searched December 20th 2012, Embase and Sociological Abstracts on January 10th 2013 and Communication and Mass Media Complete on January 24th 2013. Again, the snowball method was used to identify possible relevant articles that did not result from the electronic search.

Selection criteria

A study was selected for our study if it met all of the following criteria:

1. The publication has as (one of) its main subject(s) the package information leaflet and/or the summary of product characteristics;
2. The publication refers to potential problems with the PIL or SmPC such as finding and/or comprehending relevant information from PILs or SmPCs by patients and/or users, implications for patient safety, unclear lay-out or design, etc.;
3. The publication addresses the PIL or SmPC within the geographical context of at least one EU Member State or candidate MS, or EFTA-members; in case the publication refers to health literacy or comprehension issues regarding information on medicinal products, publications from other Western (Anglo-Saxon) countries will also be included;
4. No limit will be set on language of the summary, to enable assessment of possible summaries in languages other than English, Dutch, German, French, Portuguese or Spanish;
5. The publication is a professionally or scholarly 'sound' publication, i.e. a scientifically peer reviewed study or a publication from a governmental or professional association.

Review procedures

The first step involved screening of titles that resulted from the electronic database search. This was done by two reviewers, JdB and LvD, independent from each other. As second step, the abstracts from the selected titles were (again independently) screened by the same two reviewers on whether the selection criteria were met. Disagreements between the two reviewers were resolved by discussion. Hereafter, full texts were obtained of those articles of which the abstracts were found to be potentially relevant and of those we had insufficient information (e.g. due to lack of an abstract). The above criteria were applied to these full texts to determine whether the articles were relevant for inclusion in our study. The papers identified by snowballing were first screened by DKTR and then by LvD – again disagreements were resolved by discussion.

Data extraction

One reviewer, SPM, extracted study characteristics of each relevant article found in the initial database search (in PubMed). A second reviewer, MV, extracted these characteristics of each additional relevant article found through the PIL-s BOX study search (in PubMed, Embase, Sociological Abstracts and Communication and Mass Media Complete) and DKTR did so for the articles found through snowballing.
The following characteristics were extracted:

- General information (first author, year of publication, country)
- Objective of the study
- Involved (type of) medicine
- Positive points of PIL or SmPC
- Problems with PIL or SmPC
- Recommendations for improvement of PIL or SmPC (authors' conclusions)

3.1.2 Search for grey literature and previous literature reviews

In addition to the electronic databases covering scientific literature, a search of the so-called grey literature was conducted. The following repositories were searched for documentation about including a key information section published since 2000: Digital Repository Infrastructure Vision for European Research (DRIVER) and Scirus. Additionally, information was retrieved from contacts of the research team. We also included previous literature reviews which overlap with this review, using the knowledge of domain experts.

3.2 Results scientific literature

3.2.1 Number of included studies

The initial search in the PubMed database resulted in a total of 2,631 hits (Table 3.1). The update of this search in March 2013 provided another 492 hits. Screening of titles resulted in a total of 227 potentially relevant titles. Subsequent screening of the corresponding abstracts yielded 72 potentially relevant abstracts. The literature search for the PIL-s BOX project provided an additional 15 abstracts for the PubMed search. In the databases Embase, Sociological Abstracts and Communication and Mass Media Complete another 24 potentially relevant abstracts were selected. Of 111 abstracts, full texts were obtained. Note that full texts were also obtained for those abstracts that provided insufficient information to decide whether it was a relevant study or not. A list of studies that were excluded after reading the full text (with reason of exclusion) is provided in Appendix 1B.

The snowball method provided 18 relevant new studies. Finally, a total of 61 studies met all inclusion criteria and were included in this review (Table 3.2). Appendix 1A shows the main characteristics of the 61 included studies.

Table 3.1: Number of hits per database resulting from the electronic search, number of relevant titles and number of relevant abstracts.

Electronic database	Total hits	Unique hits	Relevant titles	Relevant abstracts PILs
Initial PubMed search	2,631	2,631	207	64[2]
Update PubMed search	492	492	20	8
Additional search PILs BOX study:				
PubMed	5,019	5,019	264[1]	15[3]
Embase	4,660	1,644*	56[1]	19
Sociological Abstracts	294	275	3[1]	1
Communication and Mass Media Complete	95	78	16[1]	4[3]
Total number of full texts	N/A	N/A	N/A	111

** Embase is known to show a large overlap with PubMed (both cover MEDLINE records)*
1 includes potentially relevant titles for both PILs and PILs-BOX project
2 includes 30 'doubt' abstracts
3 without duplicates from initial PubMed search and update

Table 3.2: Number of studies included on major topics database resulting from the electronic search, number of relevant titles and number of relevant abstracts.

Topic	Number of studies
Evaluation of PIL: comprehension and /or readability	15
Evaluation of PIL: design, lay-out and/or structure	20
Evaluation of PIL: completeness and/or consistency of information	3
Evaluation of SmPC	8
Evaluation of presentation of risk information in consumer medicines information (not specifically PIL)	4
Evaluation of the use of pictograms in medication information (not specifically PIL)	4
Evaluation of prescription drug warning labels	7

3.2.2 Comprehension and/or readability of the PIL

Overall, the studies showed that there is room for improvement regarding patients' comprehension of the PIL and its readability. A study from Sweden in which 30 leaflets (developed before 2005) were examined demonstrated that especially information about interactions and contraindications was too complex and had a low degree of comprehensibility (12). Two studies from Germany, both by Fuchs and colleagues, also examined comprehensibility of information in the PIL (mainly developed before 2005). One study examined 68 PILs of commonly used drugs and revealed that although all PILs included information about indication, contraindications, interactions, dosage instructions, adverse reactions and storage, the way in which this information was provided could be improved (e.g. 10 PILs missed information on what to do when an administration error was made, 13 PILs provided dosage instructions only in mg of active ingredient instead of unit doses) (13). In the other Fuchs study 5 model PILs were developed and compared with their original. Information about dosage instructions and possible adverse effects was least often well comprehended and located. Nine recommendations (five to give more appropriate dosing instructions and four for more appropriate side effect information) were given (14). A total of 54 leaflets were analysed in a study from Spain. It was concluded that the leaflets needed more information, especially about possible interactions, contraindications, side effects, and storage, but also about benefits of the drug (15). Hamrosi et al also found people regarded benefit information as positive, but in practice they were sometimes surprised so few would benefit (as shown by numerical benefit information in the leaflets)(16) . Vander Stichele et al (2002) found that adding a section on benefit information within a patient package insert helps to integrate increased knowledge about medication into a more balanced benefit/risk perception (17).

Shiffman et al. in the USA assessed three types of medication information - among which the PIL – for antidepressant medication and showed that especially low literate patients had problems understanding the information (18). On the other hand, Nathan et al. in the USA demonstrated that the majority of patients read the leaflet provided with a new medicine and that they found the PIL easy to understand and useful (19). In addition, PILs for antiepileptic drugs appeared readable and comprehensible for the general UK adult population according to a study conducted in the UK in 1999 (20). In 2002 Hughes et al (10) found a minority of UK patients had read the leaflet, but a later UK study in 2007 showed most people were aware of the PIL; most at least read some of it with the first supply. However, they had rarely looked at it after then – and so would not be aware if the information in the PIL had changed since they had started taking the medicine(21). Another study noted that side effects linked to a medicine were particularly likely to change over time (12). Wolf et al (2012) in the US found deficiencies in leaflets which did not provide summaries that highlights 'need-to-know' information, suggesting this would allow patients to self-tailor the amount of knowledge they want (22). They noted that also lacking was information about the purpose of the information. A paper from the linguistic domain, gave many recommendations including the use of 'you' and the imperative ('Take the tablets …')(23).

A number of studies concluded that consumers should be involved in the development and testing of PILs (6;12;24;25). However, only one paper tried to examine the impact of the legislative change in 2005, requiring 'consultation with target patient groups' (largely implemented through 'user testing') (26). This was undertaken on German PILs and found that medicines on the market since then 'show a trend towards improvement' when compared with products marketed before 2005. They noted, however, that the effect is 'barely recognisable' by patients, as only new products on the market need to be tested in most EU countries such as Germany

(although PILs for existing products were required to be tested in some other countries, such as the UK).

The need for patients to have a discussion about their medicines with a health professional, as well being given the PIL, was mentioned in some papers (11; 12; 27; 21). A specific point made that the discussion should be at the same time the PIL is given (12;27), to encourage the use of the PILs by patients (21;12).

3.2.3 Design, lay-out and/or structure of the PIL

In total, 20 studies concerned the evaluation of the PIL with regard to design, lay-out and/or structure. Many studies gave recommendations for improvement of the PIL. These included: a preference for a more detailed but schematic PIL without use of colours and a minimal point size of 10 or 11 (28); a generic structure with transparent and concise headings and low text lexical density (29); a lower reading level (below 5^{th} or 6^{th} grade) and a point size of at least 12 pt Times Roman (30); increased paper size to allow for more readable text and illustrations (31); a consistent generic structure with a positive tone, headings in the form of questions, clear vocabulary and clear instructions (32); shortening PILs and providing more precise, concise and realistic rules in guidelines, templates and directives (33). Recommended novel formats included a single page table format and/or soft edged ('bubble') boxes(34). More explicitly, both Fuchs et al. (2005) and Pander Maat & Lentz (2011) proposed a new structure of the PIL (35;36). Box 3.1 provides these recommendations. They are quite different. Whereas Fuchs et al recommend a list comparable to the what is recommended in article 11 (but in a different order), Pander Maat & Lentz propose a structure that may fit better in the perceptions of patients as it is organised around goal and usage.

Box 3.1 Recommendations on new structure (Fuchs et al 2005, Pander Maat & Lentz 2011)

Recommendations of Fuchs et al on structure of the PIL

The structure of the PIL should be (in order of importance):

- Name of medicinal product.
- Ingredients.
- Therapeutic indication and therapeutic group.
- Contraindications.
- Appropriate precautions for use and special warnings.
- Dosage instruction.
- Hints for application errors.
- Interactions.
- Possible adverse drug reactions.
- Application form and quantity of the drug.
- Storage.
- Manufacturer.
- Date of the last update of PIL.

Recommendations of Pander Maat & Lentz on structure of the PIL

Proposed leaflet structure with 4 categories:

1. Medicine – goal and ingredients includes: 'What the medicine is used for', 'Ingredients and medicine group'.
2. Usage – directions includes: 'Directions for use'
3. Usage – potential problems includes: 'Do not use or take special care', 'Side effects', 'Driving and using machines', 'Pregnancy and breast feeding'.
4. Medicine – other aspects includes: 'Packaging and appearance', 'Storage', 'Registration data'.

Raynor et al. set ten ground rules for good practice for writers of medicines information for patients, derived from a content analysis of key texts in information design (37). Box 3.2 provides those 10 ground rules, which are to resolve problems reported in the literature with regard to comprehensibility and readability.

Box 3.2 Ground rules for composing a PIL (Raynor et al 2011 (37))

1) Use short, familiar words and short sentences;
2) Use short headings that stand out from the text;
3) Use a type size as large as will fit in the available space, but retain some white space;
4) Do not fill the page with text; leave plenty of white space;
5) Use bullet points rather than continuous text to organise lists;
6) Use a conversational tone of voice, addressing the reader as you;
7) Use the active or imperative voice: e.g. "Take this medicine";
8) Use unjustified text (ragged right);
9) Bold, lower-case text is good for emphasis (words in capitals or italics are hard to read);
10) Pictures or graphics do not necessarily improve a document.

Dickinson et al (2010), from an information design background, proposed landscape leaflets with smaller columns; wide margins and more white space; clear and distinct sections; spacing that groups like elements together, and highlighting key messages with bold text and type size (38).
Pander Maat & Lentz (2010) proposed these evidence based principles (39):

- Integrate information on same topic
- Add headings to facilitate text search
- Headings which are visually discriminable (using bold, with different font sizes)
- Remove bold fonts from body text.
- Transform all sentences containing lists into introductory segment followed by bulleted list.
- Move instructions to the beginning of paragraphs and make explicit
- Leaflet structure needs to follow readers' pre-existing schemata.

3.2.4 Completeness and/or consistency of information in the PIL

One American and one Danish study studies investigated either whether the information in the PIL was consistent (40) or complete (41). American PILs covering the same generic product (captopril) appeared to contain inconsistent information which may lead to confusion (40). PILs of 15 topical prescription medications showed incompleteness of information especially regarding effects in pregnancy, nursing and geriatric patients (41). This last study provided six ways to improve drug inserts for topical medication (see table 3.2) including the advice to add contact details for a dermatologist. Raynor et al (2007) found PILs in the UK (compared with the US and Australia) had incomplete information about how to use and monitor medications and lack of clear advice about urgency of action related to side effects (mainly developed before 2005) (42). Dickinson et al (2013) found people welcomed the idea of tailored information – tailoring to their illness primarily (rather than PILs for medicines with information about all the different illnesses it could be used for), which could make the information more relevant to them and encourage them to value it (27). Overall, 6 studies specifically described missing information from the PIL (2; 3; 7; 23; 24; 42), whereas 5 studies concluded that more concise information was wanted or needed (5;26; 10; 14; 20) . In addition, one study showed both that most patients want a more detailed leaflet, and most of the same sample wanted a more 'schematic and concise' leaflet (8).

3.2.5 Evaluation of the SmPC

Six studies of which two were conducted in the US (43;44), one in Germany (45), one in Spain (46) and two in the UK (2);(47) evaluated the content of the SmPC. Two studies revealed that the SmPC was not as complete as it should be. Both the studies of Spyker et al. and Arguello et al. showed that the SmPCs missed core clinical pharmacology information (43;46). The third study showed that information on drug interactions in the SmPC was outdated and incomplete (45). In the UK, SmPCs are the most relevant source of safety data to aid prescribing of medications for Attention deficit hyperactivity disorder (ADHD) – and updated more regularly than national guidelines (48). Also in the UK, Wall et al (2009) found that SmPC information on gut decontamination in overdose of drugs for the Central Nervous System (CNS) was inadequate (2). San Miguel (2005) found information on food-drug interactions in SmPCs in Spain is sub-optimal (47).

Two studies published in 2013 looked at the physicians' ability to use and/or their opinions of SmPCs in general and developed revised formats as a result of qualitative

and quantitative feedback in the UK (49) and Germany (50). In both countries SmPCs were little used[13] and not seen as valuable; with the UK study showing that a minority of points could be found and understood to the level required for patient leaflets. Both revised versions were shown to be an improvement, and both included a 'key information' section. The German revised version included a checklist for patient information and used a tabular format. The UK revised version included a revised and simplified heading structure, which was more visible and included more sub-headings. Simple language and shorter sentences were used, along with extensive use of bullet points. Related information was placed together, and in the place readers expected to find it.

3.2.6 Medication information in general (among which the PIL)

- **Presentation of risk information**

The three UK studies in which people's interpretation of risks of medicines was investigated all revealed that the risk was grossly overestimated, especially when the verbal descriptors previously recommended by the EC to describe risks (from 'very rare' to 'very common') were used (51-53). The fourth study, which was also conducted in the UK, investigated 50 PILs to the extent in which information on adverse effects was provided. It was shown that 40% of the PILs gave no indication at all of the likelihood of adverse effects occurring (54).

- **Use of pictograms**

Four studies evaluated the use of pictorial aids in medication information to improve comprehensibility, mainly focused on supporting low literate patients. A study from the US concluded that the inclusion of pictorial-based dosing instructions to help parents with dosing infant acetaminophen (55) led to a better understanding, especially for those with low health literacy. A study from Finland that tested whether a PIL for penicillin including pictograms improved understanding of children, however, showed that the understanding was not different between the two versions (with or without these pictograms)(56).The literature review from Katz et al (2006) showed a mismatch between patients' reading skills and patient drug information, which is especially a problem for low literate patients. They concluded that using pictograms in drug information improved comprehension and adherence of patients and recommend to combine pictograms with written and oral instructions (57). Knapp et al (2005) showed that reducing size of pictograms to incorporate into some written formats adversely affects readability, and they concluded that testing for interpretation by the public is needed for all pictograms before use (58).

Prescription drug warning labels (PWLs)

Although labelling is not directly within the scope of this project, the problems that patients experience with these PWLs might be relevant as, although they are separate labels, their wording resembles some of the wording in the PIL. Three studies explored PWLs and their comprehensibility and causes for misunderstanding among individuals with a focus on low literate patients. Webb et al. showed that most text messages included in the PWL were confusing and used language that was too difficult to understand (59). Revised PWLs were provided using comprehensible icons and

[13] In the UK the preferred source was the British National Formulary, and in Germany one of the more preferred sources is the 'Rote Liste' (German drug compendium) (50)

simplified text in accordance with patient feedback from this study. Another study revealed causes for misunderstanding of PWLs, which were attributed to one or a combination of problems associated with label text, icons and colour (60). Eight opportunities for improvement were identified. In a third study on PWLs, it was shown that explicit, easy-to-read messages on the label improved rates of attendance and comprehension. Including icons, which were developed with patient feedback, further improved correct interpretation of the warnings among low literate individuals (61). Two studies by Davis et al. assessed labels for commonly used drugs. The first study identified high lexile scores (1st-grade level) used in these labels, which could result in misuse of medication (62). Only simple tasks using uncomplicated words (such as 'Take with food') were adequately interpreted. The second study investigated the language used to describe dosing and frequency of use, and concluded that explicit language using time periods (e.g. morning) rather than the number of times per day (e.g. twice) improved comprehension (63). Finally, two studies focused on teratogen warning symbols on labels. Comprehension of the label including simplified text and an icon was higher in one study (64), whereas in the other study this was not as clear. However this last study concluded that both a new symbol plus text and a new symbol-only format performed better than the existing symbol (65).

3.3 Grey literature

The search for grey literature yielded three documents which are described below.

Always read the leaflet (5)

This report "Always Read the Leaflet, getting the best information with every medicine" was produced by the UK Medicines & Healthcare products Regulatory Agency (MHRA) after they recognised problems with the quality of information in the PIL (e.g. inconsistent information, length and poor lay-out, poor communication of risks). They established a Working Group on Patient Information to address these problems and to suggest improvements – this report described their findings. The key recommendations were:

1. The views of patients should be taken into account at all stages in the development of (PILs). Usable PILs, designed to meet the needs of patients must be the aim of all those involved - not simply compliance with the law.
2. PILs should be made more usable by taking the opportunities presented by changes in the law to achieve the best possible content and presentation. To support this, new guidance on usability and on how to take account of the outcome of user consultations should be published for producers of PILs.
3. The guidelines on risk communication included in this report should be the subject of wide consultation. In particular, views should be sought on the concepts of improved order and information on side effects, headline information targeting key messages, and short statements on benefits.
4. To promote consistency and clarity in the writing of PILs, a glossary of lay terms for describing side effects should be developed, tested and enlarged over time.
5. There should be more focus on providing information for patients who have difficulty in accessing the information in the usual PIL, or who have particular needs such as those arising from sight loss or poor basic skills.
6. The information needs of children, young people and carers should receive particular attention.
7. The impact of changes in the quality of PILs as a result of this report should be monitored with the aim of continual improvement, and the supporting guidelines periodically reviewed in the light of experience.
8. Further research should be undertaken on how to provide information in PILs that meets patients' needs in today's environment. In particular, this should explore improved communication of risks and benefits, and how information can promote safe and effective use of medicines by people with diverse needs.
9. Options should be explored for improved access to PILs, including availability at or before the prescription or purchase of a medicine, and in other situations where a PIL is not currently available.
10. Steps should be taken to promote wide public awareness of PILs and their availability in alternative formats. These should include publicity about the Group's leaflet on the risks and benefits of medicines

Investigating Consumer Medicines Information Project (I-CMI)[14]

This study was commissioned by the Pharmacy Guild of Australia after anecdotal and research evidence highlighted the limited use of Consumer Medicine Information (CMI)

[14] http://guild.org.au/docs/default-source/public-documents/services-and-programs/research-and-development/Fourth-Agreement-R-and-D/Investigating-Consumer-Medicine-Information-(I-CMI)-Project/full-final-report-part-1.pdf?sfvrsn=0

in the community in Australia. This study aimed to (a) consolidate the evidence related to CMI effectiveness, (b) substantiate the validity of anecdotal evidence on CMI provision, and (c) develop and evaluate alternative CMI formats to ensure optimal effectiveness and best practice delivery in community pharmacy practice.
The researchers used an iterative process of evaluating, designing and testing alternative CMI, where development involved an information design, functional linguistic and medicine information expertise, and where the testing included user-testing, produced alternative CMI formats which performed better and were easier to read and comprehend. The development process was informed by a detailed needs analysis of the key stakeholders, including consumers and healthcare professionals.
Some of the key findings were:

- In order to improve medicine information provision, the document itself needs to be improved in parallel with attempts to increase awareness and up-skill healthcare professionals in how to optimise the use of CMI as a tool in improving consumers' quality use of medicines.
- Regulators and producers of medicine information need to involve consumers in the process of producing medicine information so that their needs and views are better reflected.
- Information design experts and the use of information design principles should be utilised in developing CMI. Content wording and readability needs to be addressed to ensure clear, concise and easy to understand documents.
- Performance rating through the process of user testing should be considered standard routine practice in order to produce high quality CMI. Additionally, consideration should be given to alternative styles and avenues of CMI provision and monitoring.

3.4 Previous literature reviews

Raynor et al. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available about individual medicines. Health Technology Assessment 2007 (66)
This review was commissioned by the UK Department of Health, through their Health Technology Assessment programme.

The key findings include that most people do not value the written medicines information they receive (largely from studies conducted pre 2005). The poor quality of many leaflets studied, in terms of content and layout, may reflect the finding that provision, more often than not, did not increase knowledge. No robust evidence was found that the information affected patient satisfaction or affected adherence. Qualitative evidence shows that patients do not see improving compliance as a function of PILs; an informed decision not to take a medicine is an acceptable outcome. This contrasts with some professionals' view that increasing compliance was a prime PIL function. There was consistent evidence that the way in which risk descriptor information is portrayed influences side-effect knowledge. Delivering risk information numerically, rather than as verbal descriptors, ensures a more accurate estimation of the probability and likelihood of a side-effect and the risk to health.

The readability of medicines information is important to patients, with concerns about complex language and poor visual presentation. Patients value the idea of information that is tailored, set in the context of the particular illness of the individual patient, and containing a balance of benefit and harm information. Very few studies addressed either issue. Most patients wanted to know about any side-effects that could arise. Some patients question the credibility of pharmaceutical industry information, although the required PIL is written according to strict regulations.

Patients would like written information to help decision-making, first for initial decisions about whether to take a medicine or not. Hence people value information about the range of treatments available (needed before the prescribing decision). Second, they need information for ongoing decisions about the management of medicines and interpreting symptoms. Patients did not want written information as a substitute for spoken information from their prescriber. Although not everyone wanted written information, those who did wanted sufficient detail to meet their needs.

Some health professionals thought that information for patients should be brief and simple. There was evidence of professional ambivalence about written medicines information; they did not always actively recommend leaflets and were in some cases reluctant to provide certain information, particularly on side-effects.

- To improve written medicines information, it is suggested that regulators and producers of written medicines information consider the following:
- Involve patients at all stages of the process, enabling their needs to be better reflected.
- Use findings on information design and content to improve the quality and usefulness of their products.
- Present risk information numerically rather than using verbal descriptors.
- Spoken information remains the priority, but should be closely linked to written information so, in the authors' opinion, health professionals should:
- Ensure written information is not used as a substitute for discussion.

- Encourage patients to use written medicines information and welcome the questions this may raise.

Narhi U. Drug information for consumers and patients – a review of the research. (67)

This review comes from the Finnish National Competent Authority and is aimed at summarising research into the dissemination of drug information intended for patients and consumers. It is based on the assumption that patients should be able to participate in decisions about their medicines. In terms of PILs, the key points are:

- Drug information given face to face is interactive and the information can easily be tailored according to patient need.
- Written drug information can decrease the amount of misunderstanding and patients can look back at it afterwards.
- PILs are often used, but patients may not understand the information completely.
- The number of people searching for drug information on the internet is increasing, but the quality of information there is uncertain.
- The readability of written drug information can be improved in relation to print size, type, colour, syntax, Braille and size of paper.
- The comprehensibility of side effect information, including their frequency, should be improved.

Koo M et al 2003 (S14P) Factors influencing consumer use of written drug information (68)

This review focused on the use and impact of written drug information on consumers, and the factors influencing its use. It concluded that WDI has the potential to increase patients' knowledge, compliance, and satisfaction. The desirable features are:

- Serif typeface, no italics, bold for emphasis, 10pt min (12 for older people)
- Arabic numerals not roman
- Colour to increase appeal & enhance text, but not to distract from it
- Good text/paper contrast
- Bullets encouraged
- Headings clear and outstanding
- Justified left only
- Line length 30-50 characters & spaces
- Paragraph indent first line
- Ample white space

3.5 Summary

The results from the literature study suggest that the PIL needs to be concise, although some people want the full information, and it is unclear who would decide what to leave out. Indeed some studies point out information which is 'missing' from PILs. The ability to 'tailor' information for an individual's individual illness and preferences is one option. In addition, the PIL needs to contain easy-to-read messages - this benefits all patients, including those with low literacy (referred to in the USA as 'universal precautions')[15].

15 Raynor DK. Health literacy- is it time to switch our focus from patient to provider? BMJ 2012; 344:e2188

Often leaflets were found to be of high lexical density, with too small a print size, and lacking a good structure. To remedy this, there are a number of studies which describe the key principles for writing and designing effective medicines information. The evidence-based recommendations from these studies will be useful when the Readability Guideline is next reviewed. It is clear that attention needs to be paid both to the words used and the structure and design of the document itself. There are new proposed structures and formats for PILs provided in a number of papers. The inclusion of textual benefit information is generally supported by stakeholders, including patients. The lack of a method of alerting people on long-term medicines to changes in the information in the PIL has been pointed out – many people only look at the PIL the first time they get a medicine.

A common theme is that consumers should be involved in the development and testing of PILs. However, the impact of such testing is difficult to interpret, because many studies were performed before the introduction of such testing and, in most countries, un-tested leaflets remain in use for older medicines. It is important that the PIL is not seen in isolation – it should be part of the overall communication process, in which spoken information from the health professional is the most important for many people.

Studies on prescription warning labels showed that the use of icons or pictograms enhanced patients' comprehensibility of the medication information, especially patients with a low literacy level. However, these pictograms need to be of sufficient size, and be user tested to ensure comprehensibility.

Furthermore, studies on the representation of risk information revealed that irrespective of the way in which this information was presented (either qualitative with terms varying from 'rare' to 'common' or quantitative with specific percentages for example varying from >10% to <0.01%) the risks were overestimated. However, this was most marked when verbal descriptors were used alone.
Regarding prescription drug warning labels, the few studies available showed that simplified text and inclusion of comprehensible icons improved patients' understanding and interpretation of these warnings.

We identified eight studies that evaluated the SmPC. They revealed that current package inserts lack some basic clinical pharmacology information, and that physicians do not currently value the SmPC as an information source. Revised structures and formats were proposed and testing in two papers.

The need for further research in all these aspects of PILs is often mentioned in the literature and this is borne out by the relatively few studies identified.

Chapter 4 Stakeholder survey - Patient Information Leaflet

This chapter describes the results of a European-wide stakeholder survey in which relevant stakeholders were asked on their opinions on shortcomings of the PIL as well as on positive points. Also suggestions for improvements were asked for.

4.1 Methods

Two consultations rounds were held. In the first round a questionnaire was developed based upon literature and guidelines. Thereafter, a second questionnaire was developed aiming at clarifying unclear aspects and getting a deeper understanding of relevant topics brought up in the first questionnaire by different stakeholders.

4.1.1 Participants

European and national representatives of the following organizations were approached:

- Patient and consumers;
- Physicians and pharmacists (health care professionals, HCP);
- Pharmaceutical industry;
- Companies undertaking user testing.

The contacts of these representatives were found through an online search of European organizations. The organizations themselves were contacted as were their members in case a contact list was available. If the list was not available, the website of the national members was searched for contacts.

For the first questionnaire, patient and consumer representatives were invited by letter, since they received a paper version of the questionnaire with 3 examples of PILs. All other representatives were approached by email only. For the follow-up questionnaire, all representatives were contacted by email and were given the opportunity to fill in an on-line questionnaire. Due to confidentiality issues, some pharmaceutical industry representatives were recruited by their European association directly.

The following actions were taken to increase the response: Two reminders were sent to participants who, at the time the reminder was sent, had not filled in the questionnaire yet. Those representatives of physicians and pharmacists organizations who did not answer to the questionnaire after two reminders, were contacted by phone by one research associate. Those who accepted to participate received a shorter questionnaire, with only the main questions – the ones that allowed answering the main research questions and aims of the PILs study - because some participants complained that the questionnaire was too long. For the follow-up questionnaire, two reminders were sent to participants who had not filled in the online questionnaire when the reminder was sent out.

Representatives of patient and consumers organizations who did not complete the first survey received a follow-up questionnaire which included the most relevant questions asked in the first survey (this could be seen as a third reminder to those representatives).

4.1.2 Questionnaires

For the first questionnaire, a paper questionnaire was sent to representatives of patient and consumer organizations. Additionally, a link to an online questionnaire was provided as well to patient and consumer representatives. All other representatives received a link to an online questionnaire, which could be accessed as many times as participants wanted. The questionnaire, written in English. The follow-up questionnaire which aimed at gathering in-depth information on some topics participants mentioned in the first questionnaire. The topics of the questionnaire relate to the assessment of content and layout of a multi-lingual mock-up, trade-offs between suggestions for improvement, benefit and tailored information for PILs, and driving under the influence new text suggested in other EU-funded project (http://www.druid-project.eu). All online questionnaires were developed using *Collector* and data were analysed in STATA version 12.1. **The questionnaires can be requested upon from the authors**.

4.1.3 Measurements linked to research questions

Content, layout and overall quality of PILs (research question W1.1 and W1.2)

From the literature it became clear that PILs could be improved with regard to their content and layout. In order to know how the respondents in our consultation judged PILs on these issues, they were asked to assess the content, layout and overall quality of PILs.

On a scale ranging from 1 "low quality" to 9 "high quality", the quality of PILs regarding content was assessed on the following aspects:
1) ease of finding information;
2) length of the text;
3) use of short sentences;
4) ease of understanding the words;
5) use of medical terms;
6) ability to understand the text for patients in general;
7) ability to understand the text for elderly patients;
8) ability to understand the text for low literate patients.

Layout was assessed on the following topics in the same scale:
1) overall organization;
2) size (length) of the PIL;
3) font size of the text;
4) space between the lines;
5) use of bold to give emphasis to important information;
6) use of capitals to give emphasis to important information;
7) use of effective headings and sub-headings;
8) easy to understand pictograms to aid the text;
9) contrast between text and background;
10) transparency of the paper (text on one side show through on the other side);
11) thickness of the paper.
Finally, an overall score was asked for, using the same 1 to 9 scale.

Respondents were equally asked to assess the content and layout of PILs of some actual examples, available on the market (hard copies as found in medicines' boxes). The example of PILs were from the following medicines (after consulting EMA): an over-the-counter medicine (medicine A, authorised after 2005), a bisphophonate (medicine B, authorised after 2005), a medicine for respiratory complaints (medicine C, authorised before 2005), a antihypertensive (medicine D, generic, authorised before 2005) and an antibiotic (medicine E; authorised before 2005). Since five examples would originate in too long questionnaires, it was decided to randomly divide respondents in two groups and each of the groups analysed 3 PILs. Group A analysed medicines A, B and C while group B analysed medicines C, D and E. Medicine C was given to all respondents, since the pharmaceutical company responsible for its marketing authorisation provided us not with the actual PIL but with a A4 document. It was decided to send this example of PIL as an alternative to the PIL, since font size was bigger and pictograms were clear.

Problems related to PILs and their consequences (research question W2.1)

Respondents were asked whether they were aware of problems concerning patients' ability to read and understand the PILs in their group / organization (yes/no). In case they were aware of problems, respondents were asked "What problem(s) are you aware of concerning patients' ability to read and understand the PIL in your patient group? Please briefly outline the problem(s) and the most important consequences of the mentioned problem(s)" (open question). Respondents' answers were thereafter grouped into three groups: 1) related to layout; 2) related to content and 3) other problems.

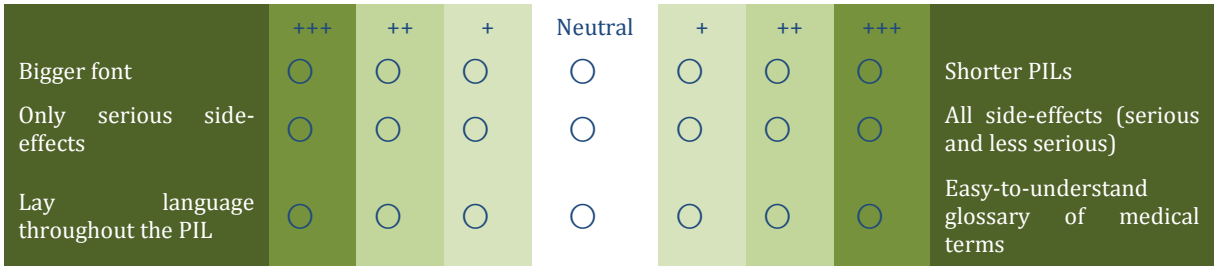
Positive points related to PILs and their consequences (research question W2.1)

Positive points can work as facilitators for improving the PIL. As such, participants were asked what they considered to be positive points related to patients' ability to read and understand the PILs, as well as the most important consequences of the positive points (open questions).

Recommendations for improvements (research question W3.1)

Recommendations for improvements of the PILs (in terms of content, design and layout) so that their value to the general public as well as their contribution to patient safety can be improved. The following question was asked "what solutions can be used to overcome the problems that affect negatively the understanding of PILs" (open question). Additionally trade-offs between different aspects of design and content were asked for in order to see which problems needed to be solved first. The question was posed as follows:

In a recent study, also conducted by our research team, some very relevant issues were brought up by our respondents, even if sometimes some issues can contradict others. Imagine, now, you would be given the opportunity make a tailor-made PIL. From the list below, what would you value more? Please keep in mind that some aspects are not necessarily opposites (only three examples of items are provided here, for others, see Appendix).



Other measurements

Characteristics of participants: country of residence, type of organization they work for, professional background, current position within their organization and whether their current work involves working with the PIL and/or SmPC.

Regulatory issues: In order to obtain a marketing authorisation for a medicinal product, applicants must include a Patient Information Leaflet in accordance with Article 58 of Directive 2001/83/EC. For the full information to be included in each section of the PIL, applicants should refer to article 59 of that same directive. To comply with the legislation, applicants can follow the Quality Review of Documents (QRD) template, provided by the European Medicines Agency (EMA). It was found pertinent to inquire participants on the QRD, since this document is of great relevance for the commercialization of medicines. For the purpose of this study, version 8 of the QRD template was used. Respondents were asked whether they knew the QRD templates, how they value the information in the templates and whether topics are missed. They were also asked to value its structure. Moreover, they were asked whether or not the QRD should be more regulated than it is now. Also patient organizations were asked whether they are aware of the obligation for patient consultation for PILs since 2005.

4.2 Participants & their characteristics

4.2.1 Response

European and national representatives of patient and consumer organizations, health care providers (physicians and pharmacists), pharmaceutical industry, and user testing companies were approached. As far as national representatives are concerned, it was made an effort to include representatives of all European countries. The total number of questionnaires used to generate results are presented in Table 4.1. For the results described in this chapter it is important to note that patient and consumer organizations' representatives who did not reply to the first questionnaire were asked

the most relevant questions from the first questionnaires in the follow-up questionnaire (n=22). These data were analysed together with the corresponding data from the first survey, meaning that for part of the questions 71 respondents could be included.

Table 4.1 - Response rate among the different stakeholders' representatives.

	Patient & Consumers		Health care providers		Pharmaceutical Industry		User testing *
	1st round	Follow-up	1st round	Follow-up	1st round	Follow-up	1st round
Number of questionnaires sent out	476	492	123	192	170 **	170 **	6
Number of questionnaires that could be used for the analysis***	49	42	33	12	123	40	6

* User testing representatives did not reply to the follow-up questionnaire.
** Some organizations forward the questionnaire directly to their members, making it impossible to know how many questionnaires were actually sent out to participants.
*** Participants who did not fill in the questionnaire or only filled in their background information were not included in the analysis.

4.2.2 Characteristics of participants

Table 4.2.a shows the characteristics of all participants in the first round and table 4.2.b for the follow-up round. Representatives of HCPs (67%) and pharmaceutical industry (72%) often had pharmaceutical background (table 4.2.a). The background of representatives of patient and consumer organizations was more varied : 41% stated that they have another professional background (than legal/medical/pharmaceutical/social). These included for example: clerical administration, economics, health science, international business, linguist and management. Current positions varied both between and within the different groups of stakeholders. Among HCPs, a management position (27%) and working as a pharmacist (41%) were most frequently mentioned. Just over half of the participants from patient and consumer organizations hold management or board position. Industry representatives most often mentioned to hold a management position (37%) or to be policy officer (24%). Participants came from all over the European Union with an overrepresentation for the UK, Germany, and the Netherlands. Also from Croatia relatively many respondents participated. Three quarter of the HCP participants represented a national organization, while pharmaceutical industry representatives were spread across all kind of organizations (national/European, worldwide). When asked for their involvement with the PIL in their daily work, most of the respondents stated that they are sometimes to always involved with the PIL (HCPs: 90%; patients and consumer organizations: 82% and pharmaceutical industry: 90%). The composition of the population in the follow up round slightly differed (table 4.2b).

Table 4.2.a: Participants characteristics in percentages per group – first round

	Health care providers	Patient Organizations	Pharmaceutical industry
Professional background			
Legal	-	2.8	-
Medical	23.3	21.1	9.8
Pharmaceutical	66.7	5.6	72.4
Social sciences / other sciences	6.7	29.6	8.9
Other	3.0	40.6	5.6
Current position			
Advisor	10.0	8.6	-
Management (including board)	26.7	51.4	37.4
Medical doctor	10.0	-	-
Pharmacist	40.7	-	16.3
Policy officer	6.7	12.9	23.6
Project manager	-	4.3	8.9
Other	3.0	20.0	13.8
Country of residence			
Baltic states	3.0	2.8	-
Belgium	3.0	7.0	1.6
Bulgaria	3.0	-	-
Croatia	3.0	7.0	4.0
Cyprus	-	1.4	-
Czech republic	-	4.2	2.4
Denmark	-	-	4.0
Finland	6.0	4.2	-
France	6.0	1.4	4.0
Germany	-	5.6	26.0
Greece	-	1.4	0.8
Hungary	3.0	-	-
Ireland	3.0	2.8	1.6
Italy	3.0	2.8	0.8
Malta	-	2.8	-
Netherlands	3.0	7.0	4.0
Poland	3.0	1.4	0.8
Portugal	6.0	7.0	1.6
Romania		2.8	-
Slovakia	3.0	-	-
Slovenia	-	5.6	-
Spain	-	2.8	9.7
Sweden	3.0	-	6.5
United Kingdom	9.0	8.4	15.8
Outside EU/other European countries	33.4	7.0	4.0

EU/Global	6.0	12.6	8.1
Unknown/no answer	-	1.4	5.6
Organisation	HCP	Patient	PI
Regional	12.5	-	4.9
National	75.0	-	33.3
European	12.5	-	30.1
Worldwide/international	-	-	26.0
Involvement with PIL			
Always	23.3	16.9	23.2
Often	30.0	26.8	30.0
Sometimes	36.7	38.0	36.7
Never	10.0	18.3	10.0
Involvement with SmPC			
Always	33.3	-	33.3
Often	20.0	-	20.0
Sometimes	33.3	-	33.3
Never	13.3	-	13.3

Health care providers: n= 33, Patient organizations: n= 71, Pharmaceutical industry: n=123

User testers (not in table, n=6)

Six user testing companies' participants were included in the survey representing European (n=5) and worldwide (n=1) companies. Their backgrounds were: pharmaceutical (n=2), clinical research (n=1), design and editorial (n=1), and visual communication (n=1). User testing companies' representatives dealt with the PILs in different ways, in terms of assessment of quality of PILs with respect to its layout (n=4) and content (n=3), compliance with regulatory guidelines (n=3) and SmPC (n=1), as well as readability testing (n=2), translation (n=1), development of other forms PILs (electronic leaflets) (n=1), editing (n=1), and design (n=1) of the PIL.

Table 4.2.b: Participants characteristics in percentages per group (2nd round)

	Health care providers	Patient Organizations	Pharmaceutical industry	Regulatory offices	Communication experts
Professional background					
Legal	-	2.4	-	-	-
Medical	16.7	21.4	9.8	18.8	-
Pharmaceutical	50.0	4.9	68.3	81.2	25.0
Social sciences	25.0	26.2	4.9	-	12.5
Other	8.3	45.2	17.1	-	62.5
Current position					
Advisor	16.7	14.3	2.4	6.3	-
Management	-	23.8	22.0	12.5	12.5
Medical doctor	8.3	2.4	2.4	12.5	-
Pharmacist	16.7	-	14.7	37.5	-
Policy officer	-	7.1	4.9	-	-
Project manager	8.3	-	14.6	-	-
Other	50	52.4	39.0	31.3	87.5
Country of residence					
Baltic states			2.4		
Belgium	8.3	7.1	4.9		
Bulgaria		2.4		6.3	
Croatia		2.4			
Cyprus		2.4			
Czech republic		4.9	2.4	6.3	
Denmark			2.4	6.3	
Finland		2.4	4.9		
France			4.9	6.3	
Germany		7.1	17.1		
Greece			2.4		
Hungary				6.3	
Ireland	16.7	2.4	2.4		
Italy		2.4			
Malta		2.4		6.3	
Netherlands	16.7	9.5	2.4		25.0
Poland		2.4	2.4	6.3	
Portugal	8.3	9.4	2.4		
Romania			2.4	6.3	
Slovakia	8.3		2.4		
Slovania				6.3	
Spain		7.1	7.3		
Sweden	16.7		2.4	12.5	
United Kingdom	8.3	9.5	9.8	6.3	62.5

Outside EU	16.7	11.9	7.3	12.5	12.5
EU/Global		11.0	9.8		
Unknown/no answer		2.4	7.3		
Organisation					
Regional	16.7	2.4	12.2	-	-
National	58.3	71.4	24.4	100	37.5
European	16.7	19.0	26.8	-	-
Other	8.3	7.1	36.6	-	62.5
Involvement with PIL					
Always	8.3	11.9	53.7	62.5	87.5
Often	33.3	28.6	31.7	31.3	12.5
Sometimes	41.7	33.3	14.6	6.3	-
Never	16.7	26.2	-	-	-
Involvement with SmPC					
Always	8.3	-	56.1	56,25	37.5
Often	41.7	-	31.7	37,5	25
Sometimes	16.7	-	12.2	6,25	12.5
Never	33.3	-	-	-	25

Health care providers: n= 12, Patient organizations: n= 42 , Pharmaceutical industry: n=40, Regulatory offices: n= 16, Communication experts: n= 8

4.3 Content and layout of PILs

4.3.1 Judgement on content and layout

To assess content and layout of PILs participants were asked to judge PILs in general, five specific examples and a multilingual mock-up. The included PILs covered of a variety of medicines, as selection was based upon the following opposing characteristics: chronic versus acute, OTC versus prescription only, before 2005 versus after 2005, centralised procedure versus decentralised procedure and multisource versus single source. Once receiving the PILs they proved to have quite a different lay-out from a long black and white PIL printed on thin paper to a full-coloured booklet on shiny thick paper.

Judgement of PILs in general

To obtain an idea of how respondents view PILs we first asked for a judgement on PILs in general. The results of this assessment are presented in Table 4.3. On a scale from 1 to 9, the overall quality of PILs received an overall quality rating between 4.3 (user testing companies' representatives) and 5.5 (HCP organizations' representative), meaning that overall respondents feel that there is room for improvement. Scores for lay-out and content did no differ much.[16]

[16] Sum scores were calculated for judgment of different aspects of layout and quality

Table 4.3 – Assessment of content, layout and overall quality of PILs (in general) by different stakeholders (first consultation round).

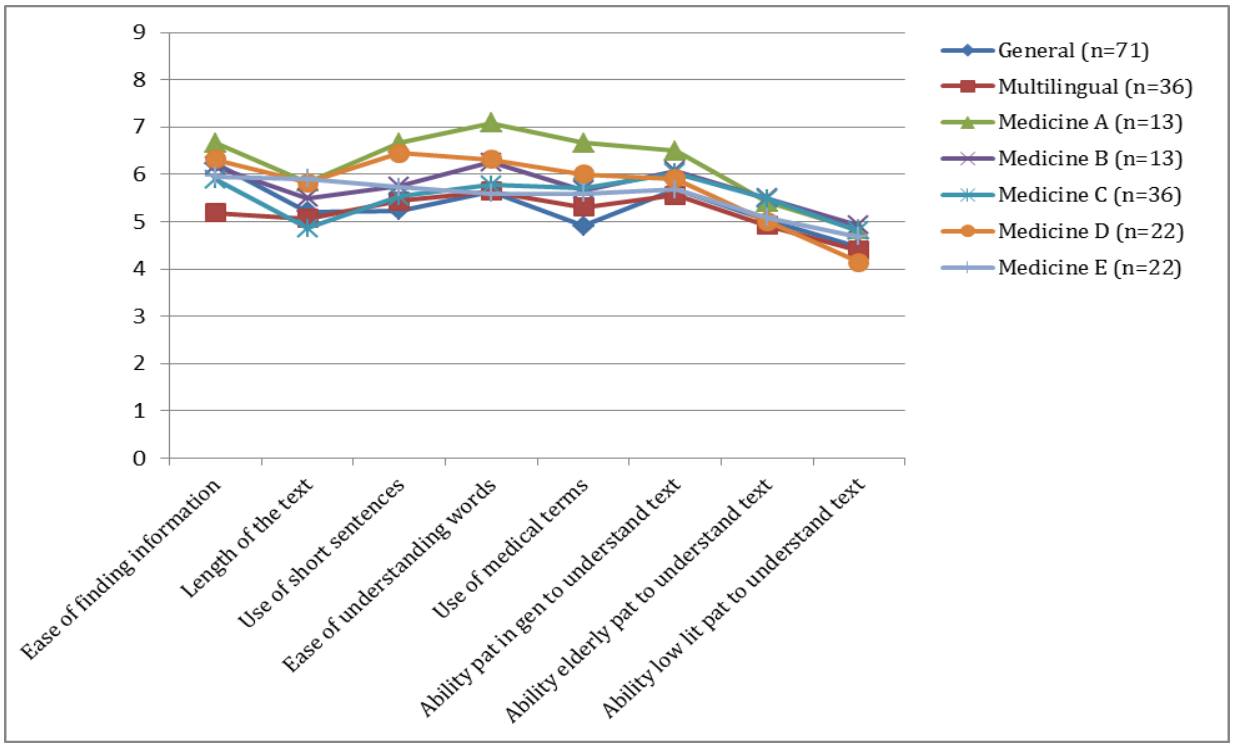
	Representatives of patient and consumer organizations	Representatives of health care providers organizations	Representatives of user testing companies
Rating content*	N = 71 Mean = 5.3 ± 2.1 CI = 4.8 to 5.8 α (scale) = 0.95	N = 24 Mean = 5.1 ± 1.7 CI = 4.4 to 5.8 α (scale) = 0.93	N = 4 Mean = 3.4 ± 2.2 CI = -0.0 to 6.8 α (scale) = 0.98
Rating layout*	N = 70 Mean = 5.6 ± 19 CI = 5.1 to 6.0 α (scale) = 0.95	N = 24 Mean = 5.4 ± 0.61 CI = 4.7 to 6.1 α (scale) = 0.93	N = 4 Mean = 3.5 ± 2.0 CI = 0.4 to 6.6 α (scale) = 0.97
Rating overall quality*	N = 70 Mean = 5.3 ± 1.9 CI = 4.8 to 5.7	N = 32 Mean = 5.5 ± 2.0 CI = 4.8 to 6.3	N = 4 Mean = 4.3 ± 1.7 CI = 1.5 to 7.0

* Scale ranging from 1 "low quality" to 9 "high quality".
Note: pharmaceutical industry representatives did not assess content, layout and overall quality of PILs.

Five examples of PILs

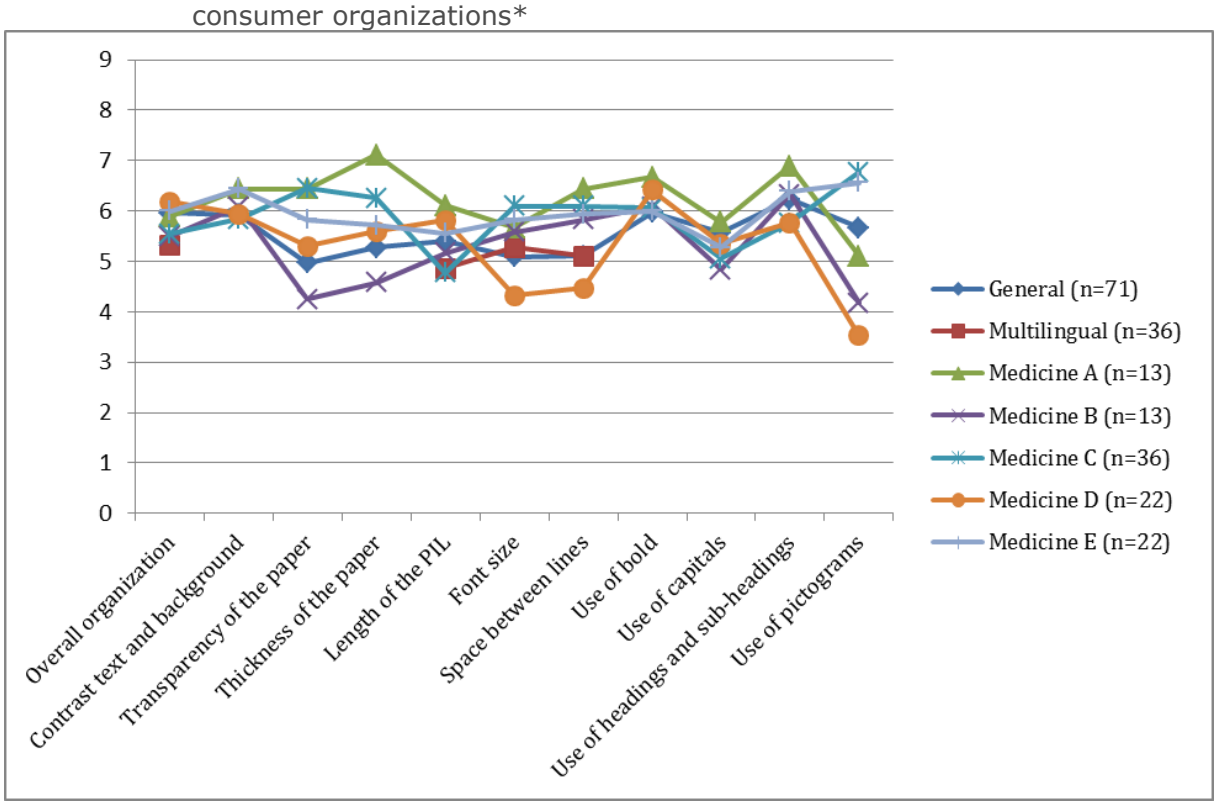
Representatives of patient and consumer organizations were asked to rate 5 real examples and a multilingual mock-up on the same scale (1 to 9). On average, the PIL with higher rating scores for the quality of content, layout and overall quality was a full-coloured booklet (mean scores of 6.2, 6.2, 6.7 respectively). This PIL was issued after user testing was introduced. The one with lower scores was the multilingual PIL mock-up (mean scores of 5.2 for content, 5.1 for layout and 5.3 for the overall quality). Still, the patterns of rating of the overall quality of PILs in general was the same as for the multilingual PIL (mean score of 5.3).

Figure 4.1a: Assessment of content of PILs by representatives of patient and consumer organizations*



*) 1= very low quality; 9= very high quality

Figure 4.1b: Assessment of **layout** of PILs by representatives of patient and consumer organizations*



*) 1= very low quality; 9= very high quality

Multilingual PIL

We asked participants who were familiar with multilingual PILs whether they would prefer to provide separate PILs for each language. Just over one third of the patient and consumer representatives are in favour of the use of one language PILs provided separately in countries with more than one official language. Half of the HCPs agreed on this, and only a small minority of the pharmaceutical industry representatives. Respondents who preferred one language PILs over one multilingual PILs did it mainly because they felt it was easier to find the information in PILs with only one language (84.6% P; 83.3% HCP; 100% pharmaceutical industry representatives; data not in table).

Table 4.4 – preference for multilingual versus single-lingual PILS (follow up round)

	Representatives of patient and consumer organizations	Representatives of health care providers organizations	Representatives of pharmaceutical industry
Use of one language PILs, provided separately, in countries with more than 1 official language	N = 36 In favor – 13; 36.1% Against – 15; 41.7% Doesn't matter – 8; 22.2%	N = 12 In favor – 6; 50.0% Against – 3; 25.0% Doesn't matter – 3; 25.0%	N = 30 In favor – 4; 13.3% Against – 24; 80.0% Doesn't matter – 2; 6.7%

4.3.2 Specific issues on content

Information for specific target groups

PILs focus on all users of a medicine. For some specific target groups extra information may be needed. We asked respondents for a variety of target groups whether PILs in general include sufficient information for these groups (Table 4.5). A majority of the representatives of the pharmaceutical industry and user testers think that these needs are sufficiently addressed in the PIL. The exception is for user testing companies' representatives: regarding the information for children and infants their opinion is inconclusive. HCP organizations' representatives are more sceptical. A majority of them thinks that there is not enough information for elderly and patients with more than one illness in the PIL; their opinion on information on children and infants is inconclusive.

Information that is currently missing in the PIL

Respondents were asked what information they currently miss in the PIL which could improve patients' ability to read and understanding the PIL. Appendix 2 summarises the answers respondents gave to this open-end question. The answers show a very varied (and non-consistent) picture, for example relating to specific topics that were missing (for example on allergies or lifestyle advises), to the addition of pictograms and pictures, and the inclusion of (risk-)benefit information.

Table 4.5 – Is the information encompassed in the PILs sufficient for specific target groups? Stakeholders' answers (in percentages) (first round)

	Representatives of health care providers organizations (N=32)	Representatives of pharmaceutical industry (N=123)	Representatives of user testing companies (N=6)
Elderly	Yes – 12; 37.5% No – 14; 43.8% Don't know – 6; 18.8%	Yes – 90; 73.2% No – 29; 23.6% Don't know – 4; 3.3%	Yes – 5; 83.3% No – 1; 16.7%
Patients with co-morbidities	Yes – 8; 25.0% No – 18; 56.3% Don't know – 6; 18.8%	Yes – 68; 55.3% No – 40; 32.5% Don't know – 15; 12.2%	Yes – 4, 66.7% No – 2; 33.3%
Pregnant women	Yes – 24; 75.0% No – 7; 21.9% Don't know – 1; 3.1%	Yes – 103; 83.7% No – 17; 13.8% Don't know – 3; 2.4%	Yes – 5; 83.3% No – 1; 16.7%
Women breastfeeding	Yes – 23; 71.9% No – 7; 21.9% Don't know – 2; 6.3%	Yes – 104; 84.6% No – 17; 13.8% Don't know – 2; 1.6%	Yes – 5; 83.3% No – 1; 16.7%
Children	Yes – 18; 56.3% No – 11; 34.4% Don't know – 3; 9.4%	Yes – 79; 64.2% No – 33; 26.8% Don't know – 11; 8.9%	Yes – 3; 50.0% No – 3; 50.0%
Infants	Yes – 15; 46.9% No – 13; 40.6% Don't know – 4; 12.5%	Yes – 74; 60.2% No – 38; 30.9% Don't know – 11; 8.9%	Yes – 3; 50.0% No – 3; 50.0%
Patients with long term illness	Yes – 15; 46.9% No – 10; 31.3% Don't know – 7; 21.9%	Yes – 58; 47.2% No – 45; 36.6% Don't know – 20; 16.3%	Yes – 4, 66.7% No – 2; 33.3%

Inclusion of benefit information

The inclusion of benefit information was mentioned by representatives of all stakeholder groups as being necessary to improve patients understanding of the PIL. As such, it was decided to inquire participants further on this topic in the follow-up questionnaire. Half of the representatives of patient and consumers organizations (18 out of 36), about 40% (5 out of 12) of representatives of HCP organizations and around 45% (14 out of 30) of representatives of pharmaceutical industry were in favour of the inclusion of more benefit information in PILs. Reasons why the inclusion of such information is important mentioned by the respondents were:

- it may improve adherence to medication/treatment (60.0% HCP; 35.7% pharmaceutical industry; 17.7% patients representatives);
- people need to know about benefits to be able to make an informed decision regarding their medicine (64.7% patients; 40.0% HCP; 28.6% pharmaceutical industry representatives);

- to balance the negative information in PILs (17.7% patients; 14.3% pharmaceutical industry).

Next, three different examples on how to present benefit information were suggested to participants. Half of the representatives of patient and consumer organizations and of pharmaceutical industry representatives prefer presentation of benefit information in general terms about how the medicines work (see Box 4.1 for examples and answers), an option preferred by 41.7% of the HCPs. A larger proportion of this group is in favour of the benefit information being presented in wording about the likelihood of benefit. All stakeholder groups least preferred the idea of benefit information being presented in numerical data.

Box 4.1 Examples to present benefit information (plus answers; follow up round)

The examples on how to formulate the benefit information and the answers given by participants:

- Presentation of benefit information in general terms about how the medicine works e.g. *this medicine is used to reduce the level of cholesterol in your blood*.
  - *Patient and consumers organizations – 18 out of 35; 51.4%*
  - *Pharmaceutical industry – 15 out of 30; 50.0%*
  - HCP organizations – 5 out of 12; 41.7%

- Presentation of benefit information in wording about the likelihood of benefit e.g. *this medicine can reduce the chance of you having a heart attack*.
  - *HCP organizations – 7 out of 12; 58.3%*
  - Pharmaceutical industry – 12 out of 30; 40.0%
  - Patient and consumers organizations – 8 out of 35; 22.9%

- Presentation of benefit information in numerical data e.g. *if 20 people like you take this medicine for 5 years, 1 of them will be stopped from having a heart attack or stroke*.
  - Patient and consumers organizations – 6 out of 35; 17.1%
  - Pharmaceutical industry – 1 out of 30; 3.3%
  - HCP organizations – 0 out of 12; 0.0%

Special example: driving-impaired medicines

On request of DG Sanco we asked respondents to compare two ways of expressing warnings regarding the influence of a medicine on driving fitness and operating machines, as present in the SmPC template (see box 4.2) (follow-up round). The first example was the current text in the SmPC template and the second example was a text proposed within a large European project "Driving under the Influence of Drugs, Alcohol and Medicines" (DRUID).[17] The majority of respondents preferred the current SmPC text above the proposed alternative: 57.1% of the patient organizations (n=35), 91.7% of the HCPs (n=12) and 73.3% of the pharmaceutical industry representatives (n=30). Example B was preferred by 25.7% of the patient organizations, 8.3% of the HCPs and 10% of the pharmaceutical industry representatives. The rest of the respondents was almost equally divided between "both" and "neither".

Box 4.2 Examples to express warnings on DIMs

Example A (Current SmPC text)
Medicine X has <no or negligible>, <minor>, <moderate> or <major> influence on the ability to drive and use machines.

Example B (alternative SmPC text)
Medicines without a potential relevant influence on driving (no, negligible or minor influence) or medicines with a potential relevant influence on driving (moderate or major influence).

4.3.3 Lay-out related issues

Highlighting important information

Participants were asked in what way information can be highlighted, for example by using text boxes, different text colours, bigger font, different letter types or any other alternative. The preference for the best way of highlighting important information depended greatly on the stakeholder type (Table 4.6). Representatives of patient and consumer organizations usually prefer more than one way to highlight information. Their top 3 includes: bigger font (63.1%), text boxes (60.0%) and different letter types (60.8%). The top 3 of pharmaceutical industry representatives is: different letter types (51.2%), text boxes (50.0%) and bigger font (38.4%). User testers prefer different colour texts.

[17] In the questionnaire we added "Please keep in mind that, when adding this information in the PIL the text will be "translated into meaningful colloquial language for the patient".

Table 4.6 – Preferred ways of highlighting important information in the PILs.

Representatives of patient and consumer organizations (N=65)	%
Bigger font	63.1%
Text boxes	60.0%
Different letter types	60.8%
Different text colours	47.7%
Others	10.8%
Representatives of pharmaceutical industry (N=86)	
Different letter types	51.2%
Text boxes	50.0%
Bigger font	38.4%
Different text colours	27,9%
Others (only answers by > 1 respondent expressed): Clear and good general structure of the PIL (n=6); Reduce the amount of information provided (n=5); Bullet points (n=4); Bold (n=2); Use of pictograms or pictures (n=2); Underline (n=2).	36.1%
Representatives of user testing companies (n=5)	
Different text colours	n=4
Bigger font	n=4
Different letter types	n=2
Text boxes	n=0
Others Underlined; Only bold print but no capitals or italic; Boxes, underline, capitals are proven to reduce legibility.	n=4

4.3.4 Digital alternatives for the PIL

Since we are living in a digital era, with rapid access to information from almost all places, participants were asked for their opinion on additional electronic alternatives to the paper PIL –
without being our intention to propose to replace the paper PILs. Participants were given the following alternatives: online via link to websites provided in the medicine's box, provided by pharmacists or by doctors, as well as a bar code to be scanned with a *smartphone* with direct access to the online PIL. Both respondents from patient and consumer organizations (N=64) and pharmaceutical industry (N=86) considered a link to a website provided in the medicine' box as the best alternative to the paper PILs (65.6% and 79.1%, respectively); for user testing companies' representatives (N=5), the best alternative to paper PILs were the link to a website provided by the pharmacist (80.0%) and the bar code to be scanned with a *smartphone* (80.0%). Across all groups, the use of a link to a website provided by the doctor was the less preferred alternative to paper PILs (21.9% patient and consumers organizations; 34.9% pharmaceutical industry, and 40% user testing companies).

Despite being positive about the dissemination of electronic PILs, respondents from patient and consumer organizations stressed that the electronic version can only be seen as an addition to paper PILs since not all patients will be able to access the internet and elderly and low educated patients are particularly vulnerable to electronic information. Pharmaceutical industry representatives believed that a print out from

the pharmacist is also a valid alternative to the paper PIL, currently included inside the medicine's box. However, experience of pharmacist print-out leaflets as a method of distribution has been shown to have its limitations in the USA and Australia.

4.4 Problems & consequences and positive points

4.4.1 Perceived problems & consequences

Participants were asked whether they were familiar with problems concerning patients' ability to understand the PIL and, in affirmative case, to describe the main problems they could point out, along with its consequences for the patient.

The majority of respondents from all stakeholders' groups were aware of problems that negatively affect patients' understanding of the PIL: 83.3% (5 out of 6) user testing companies; 76.3% (90 out of 118) pharmaceutical industry; 62.5% (20 out of 32) of HCP organizations, 60.0% (42 out of 70) of patient and consumers' representatives. For 28.1% (9 out of 32) of HCP and 27.1% (19 out of 70) patient and consumer organizations' representatives these problems were unknown. Respondents' opinion regarding problems affecting vulnerable groups, such as the elderly and patients with low literacy are described in Table 4.7. In general terms, participants believe that the problems affecting understanding of the PILs are the same for elderly and low literate as for patients in general (the only exception is for representatives of HCP organizations who have their opinions more divided regarding elderly patients).

The problems concerning PILs mentioned by participants (answering an open ended question) are displayed in Appendix 2. These relate to both content and lay-out and generally confirm the evidence from scientific literature (chapter 3) meaning that with regard to content PILs are considered to be too difficult and to use too many medical terms, that there is too much text and there are too many side-effects mentioned. With regard to lay-out the small font and the length of the PIL are often mentioned. Representatives of the pharmaceutical industry also mention the QRD template (n=9) and liability issues (n=9) as problematic issues with regard to the PIL. In case respondents mentioned problems, we asked them what the consequences of these problems were. The following consequences were commonly mentioned by all stakeholder groups:

- Readers give up reading withholding them from important information.
- Not reading or not understanding the information in the PIL may lead to inappropriate actions such as adherence to their treatment (bot intentionally and unintentionally).
- Patient may get confused or worried for example because of the extensive list of side-effects
- People may event start distrusting medicines: 'if they can't be bothered to provide decent instructions, why should I trust this medicine?'

4.4.2 Positive points of the PILs

Almost half of the patient and consumer organization representatives (47.7%) mentioned positive points of the PIL whereas an equal number of participants could not. Similar percentages were found among representatives of HCP organizations: 50% (11 out of 22) could enumerate positive aspects and 40.9% (9 out of 22) could not. On the other hand, the majority (67.3%; 72 out of 107) of representatives of pharmaceutical industry mentioned positive aspects against 29.0% (31 out of 107) to whom it was unknown any positive points facilitating patients' understanding of PILs. All five participants representing user testing companies could give examples of positive points. However, at it seemed that positive points mentioned by respondents were wishes these respondents had for improvement rather than actual positive points, we do not further elaborate on these findings. [18]

[18] An extensive table with answers on positive poins can be requested from the authors.

Table 4.7 – Are the same problems affecting the elderly and low literate patients the same as for general patients? Stakeholders' answers (first round)

		Representatives of patient and consumer organizations (N=44)	Representatives of health care providers organizations (N=22)	Representatives of pharmaceutical industry (N=107)	Representatives of user testing companies (N=6)
Elderly patients	Same problems as mentioned for general patients	22; 50.0%	10; 45.5%	66; 61.7%	4; 80.0%
	Other problems	12; 27.3%	7; 31.8%	41; 38.3%	1; 20.0%
	I am not aware of any problems affecting elderly patients	10; 22.7%	5; 22.7%	0	0
Patients with low literacy	Same problems as mentioned for general patients	26; 59.1%	11; 50.0%	71; 66.4%	4; 80.0%
	Other problems	4; 9.1%	7; 31.8%	36; 33.6%	1; 20.0%
	I am not aware of any problems affecting patients with low literacy	14; 31.8%	4; 18.2%	0	0

4.5 Regulatory issues

4.5.1 QRD-template

To comply with the requirements in the legislation, applicants for authorisation of a medicinal product should follow the Quality Review of Documents (QRD) template, provided by the European Medicines Agency (EMA). For the purpose of this study, version 8 of the QRD template was used. HCP organizations' representatives were not asked regulatory questions concerning the PILs in order to keep the length of their questionnaire reasonable. More than half of the representatives of patient and consumer organizations (24 out of 44; 54.6%) were not familiar with the QRD-template. Regarding the information covered in this template, patient and consumer organizations' representatives were the ones rating it with higher scores in terms of its importance, on a scale ranging from 1 "redundant" to 5 "very important" (n=57; mean score = 4.6, S.D = 0.53), followed by representatives of the pharmaceutical industry (n=103; mean score = 4.2; S.D = 0.93) and user testing companies (n=5; mean score = 3; S.D = 2).

The information encompassed in the QRD, either related to its content or structure, is highly regulated. Therefore, we were interested in knowing whether participants would like to have the QRD more or less (or the same) in terms of its content and structure. The results are presented on Table 4.8, where it can be seen that the majority of the representatives of all stakeholders would like to keep the QRD template regulated as it is now in terms of its content and structure, except for the content of the QRD which, in the eyes of representatives of pharmaceutical industry should be less regulated.

Table 4.8 – Content and structure of the QRD template – should it be more or less regulated? (first round)

		Representatives of patient & consumer organizations (N=65)	Representatives of pharmaceutical industry (N=103)	Representatives of user testing companies (N=5)
Content of QRD template	More regulated	12; 18.5%	11; 10.7%	0
	Less regulated	2; 3.1%	46; 44.7%	2; 40.0%
	The same	38; 58.5%	40; 38.8%	3; 60.0%
	No opinion	13; 20.0%	6; 5.8%	0
Structure of QRD template	More regulated	13; 20.3% *	2; 2.20% **	0
	Less regulated	2; 3.1% *	16; 17.6% **	1; 20.0%
	The same	29; 60.9% *	70; 76.9% **	3; 60.0%
	No opinion	10; 15.5% *	3; 3.30% **	1; 20.0%
	* n=64, ** n=91			

The reasons for preferring a more or less regulated QRD template were diverse. With regard to the content representatives of patient and consumer organizations mention that more regulation may be needed for safety reasons, while representatives of the pharmaceutical industry plea for similarity of PILs in all EU-countries. Reasons why the

template could be less regulated according to representatives of the pharmaceutical industry refer mainly to the fact that for different products different information needs to be stressed, which may be easier in case there would be more flexibility. With regard to the lay-out of the PIL allowing electronic versions is mentioned by the pharmaceutical industry.

Since the QRD template encompasses the sections that should be included in the PILs, participants where asked for their opinion regarding the inclusion of missing sections, as well as the exclusion of other sections from the template. The majority of the representatives of patient and consumer organizations (28 out of 43; 65.1%) and pharmaceutical industry (71 out of 89; 79.8%) felt that no sections are missing in the QRD nor should be excluded (28 out of 44; 63.6% of patient and consumer organizations' representatives and 65 out of 89; 73.0% of pharmaceutical industry representatives). User testing companies' representatives, were divided. We asked respondents what sections could be added or excluded from the QRD template. The section most frequently mentioned to be excluded is the (list of representatives of the) market authorisation holders (n=18; different stakeholders) and the introductory paragraphs (n=5 representatives of pharmaceutical industry). Information on benefits is most often mentioned as missing in the QRD template (n=5 representatives of pharmaceutical industry).

4.5.2 Regulation of OTCs

According to the majority of representatives of patient and consumer organizations (39 out of 44; 88.6%) and pharmaceutical industry (58 out of 87; 66.7%), OTC medicines should be regulated the same way as prescription medicines. The percentage of representatives of pharmaceutical industry mentioning they would prefer the OCT medicines to be regulated different from prescription medicines was higher (23 out of 87; 26.4%) when compared to patient and consumers organizations' representatives (3 out of 44; 6.8%). Pharmaceutical industry representatives believed that due to the fact that OTC medicines are easily accessible to patients and that theoretically patients may not receive any information from a HCP, the OTC PILs should contain quite comprehensive information to compensate the fact that there is no doctor involved in the process. As such, respondents stressed that these PILs should focus on some information, namely:

- how to take the medicine;
- more detailed dosage instructions so that the patient can manage the dosage themselves – some respondents believe that this section should come earlier due to its importance;
- duration of use;
- information about side-effects and interactions with other medicines should be limited to the most relevant symptoms;
- adverse drug reactions which can't be diagnosed by the patient should be avoided. Instead simple words should be used to convince patients to get professional help;
- consequences of misuse;
- should be very clear to patients when to seek medical advice;

In summary, these respondents find that PILs of OTC medication should be more detailed about the precise indications and conditions of use, and possible factors influencing safety and efficacy, like other treatments, adjacent conditions, or genetic factors, as they will not be prescribed.[19]

[19] User testers (n=5) were divided in their preference regarding regulation of OTC medicines. None of the respondents explained their answer.

4.5.3 User testing

Since October 2005 it is required that for all marketing authorisations information on patient consultation has to be included in the application dossier. One way to consult patients is by user testing. Patient and consumer organizations were asked whether they knew this. Remarkably 80% (36 out of 45) of the representatives of patient and consumer organizations were not aware of this requirement. From those nine representatives who were aware of the requirement of user testing, eight answered that it led to some (n=6) or many (n=2) improvements. Those who saw improvements answered that user testing leads to leaflets that are better organised and more reader friendly. This is consistent with the findings in the literature study (chapter 3).

4.6 Solutions to further improve the PIL

4.6.1 Solutions mentioned by stakeholders

Stakeholders were finally asked what can be done to improve the PILs and make them more readable and understandable for patients. Table 4.9 summarises the suggested improvements for PILs, by representatives of patient and consumer organizations and pharmaceutical industry. Content-related solutions suggested include for example the use of lay language, including less information and shorter and simpler sentences. Suggested lay-out related solutions include bigger font, shorter PILS and a better design. With regard to other solutions, five representatives of patient and consumer organizations suggest a training for patients to read the PIL. The most frequently mentioned other solution by representatives of the pharmaceutical industry refers alternatives for the paper PIL. Most of these solutions are in line with the recommendations provided in the literature (see chapter 3).

Table 4.9 – Summary of the suggested improvements that could be done to increase patients' readability and understandability of the PIL (all suggestions done by > 1 participant) (FIRST ROUND)

Representatives of patient and consumer organizations	Representatives of pharmaceutical industry
Content – related improvements Use of lay language (n=8) Less information (n=5) shorter sentences (n=3) Layout – related improvements bigger font (n=7) better design (n=4) highlight important information (n=2) Other improvements Training patients how to read PIL (n=5) Pictograms (n=5)	Content – related improvements Less information (n=12) Use of lay language (n=8) Shorter and simpler sentences (n=7) Limit the PIL to the information that the user requires for the daily use of the medicine (n=3) Layout – related improvements Highlight important information (n=3) Better layout (n=2) Other improvements Use alternatives ways to the paper PIL, namely, use of an online PIL (*e*PIL) (n=13) Harmonization of structure and content (n=2)

4.6.2 Trade-offs between potential solutions to improve the PIL

Considering the solutions presented by the respondents, some are virtually impossible to combine, such as increasing the font of the text used in the PIL and, at the same time, decreasing the length of the PIL. To get a grasp of what is more important for respondents, in the follow-up questionnaire, representatives of patient and consumers (N=36), HCPs (N=12) and pharmaceutical industry (N=30) were asked to weigh different aspects (Figures 4.2 to 4.4). In the three graphic representations below, the vertical axes are the two criteria participants had to weigh up against each other. The frequencies (number inside each bar) which correspond to the percentage presented in the horizontal axis.

In all stakeholder groups a shorter PIL is preferred above a longer PIL and a bigger font above a smaller font. Representatives of patient and consumer organizations and HCPs prefer more space between the lines. When asked to make a trade-off between these three characteristics (length, font, line spacing) it becomes clear that representatives of patient and consumer organizations and HCPs prefer a bigger font and more spacing between the lines above having a shorter PIL. HCPs have a preference for a bigger font above a shorter PIL Pharmaceutical industry representative views are inconclusive.

With regard to the trade-off between more benefit information versus more warning information representatives of patient and consumer organizations and the pharmaceutical industry are inconclusive. HCPs prefer more warning information or are neutral. Additionally. representatives of patient and consumer organizations prefer to have all side effects mentioned in the PIL as do representatives of the pharmaceutical industry. HCPs are inconclusive in this respect. Representatives of patient and consumer organizations and HCPs prefer a potential key information section at the beginning of the PIL above an index, while the pharmaceutical industry is inconclusive. Finally, while HCPs and pharmaceutical industry representatives prefer lay language above a glossary with explanation of medical terms, representatives of patient and consumer organizations are inconclusive.

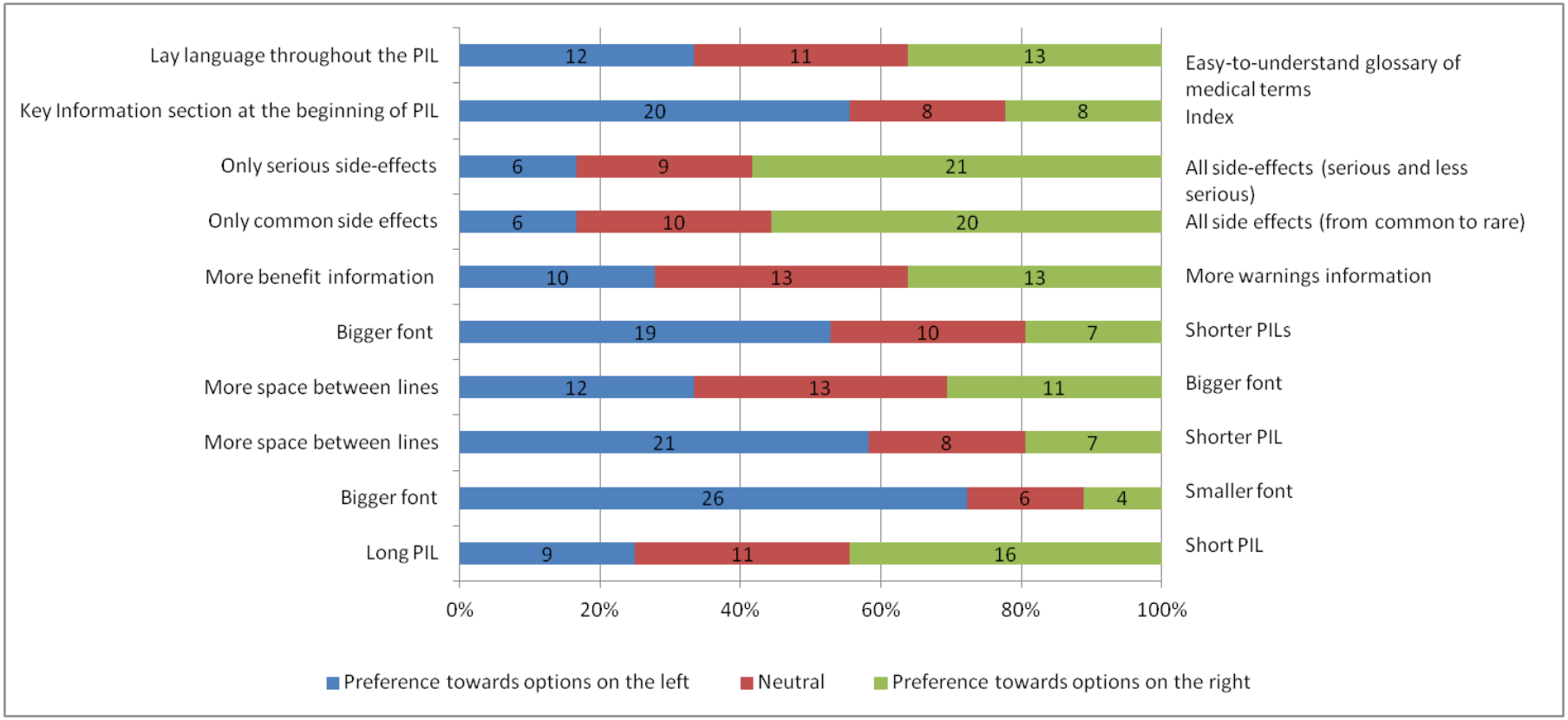


Figure 4.2 – Patient and consumer organizations representatives' preference when weighting different topics related to content and layout of PILs.

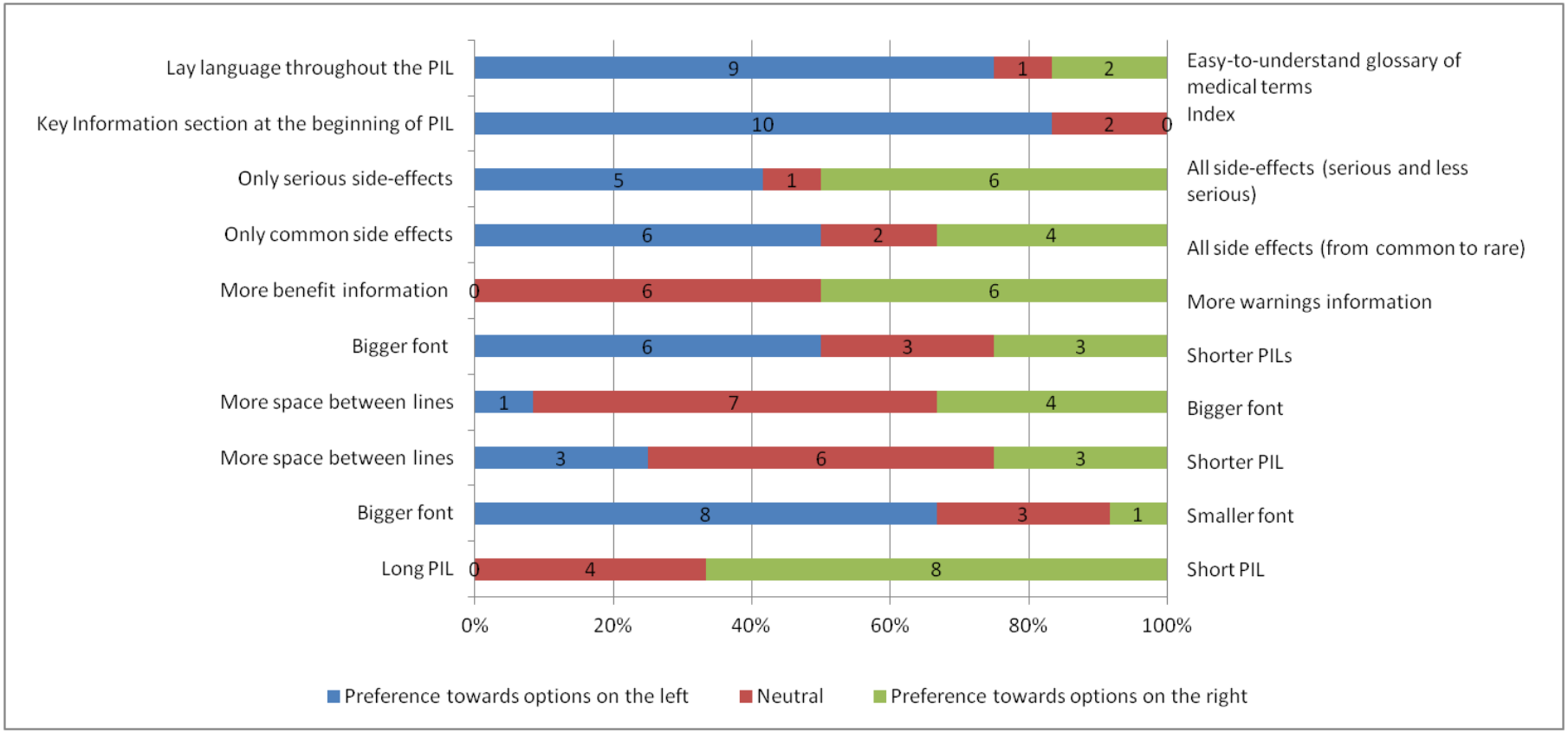


Figure 4.3 – HCP organizations representatives' preference when weighting different topics related to content and layout of PILs.

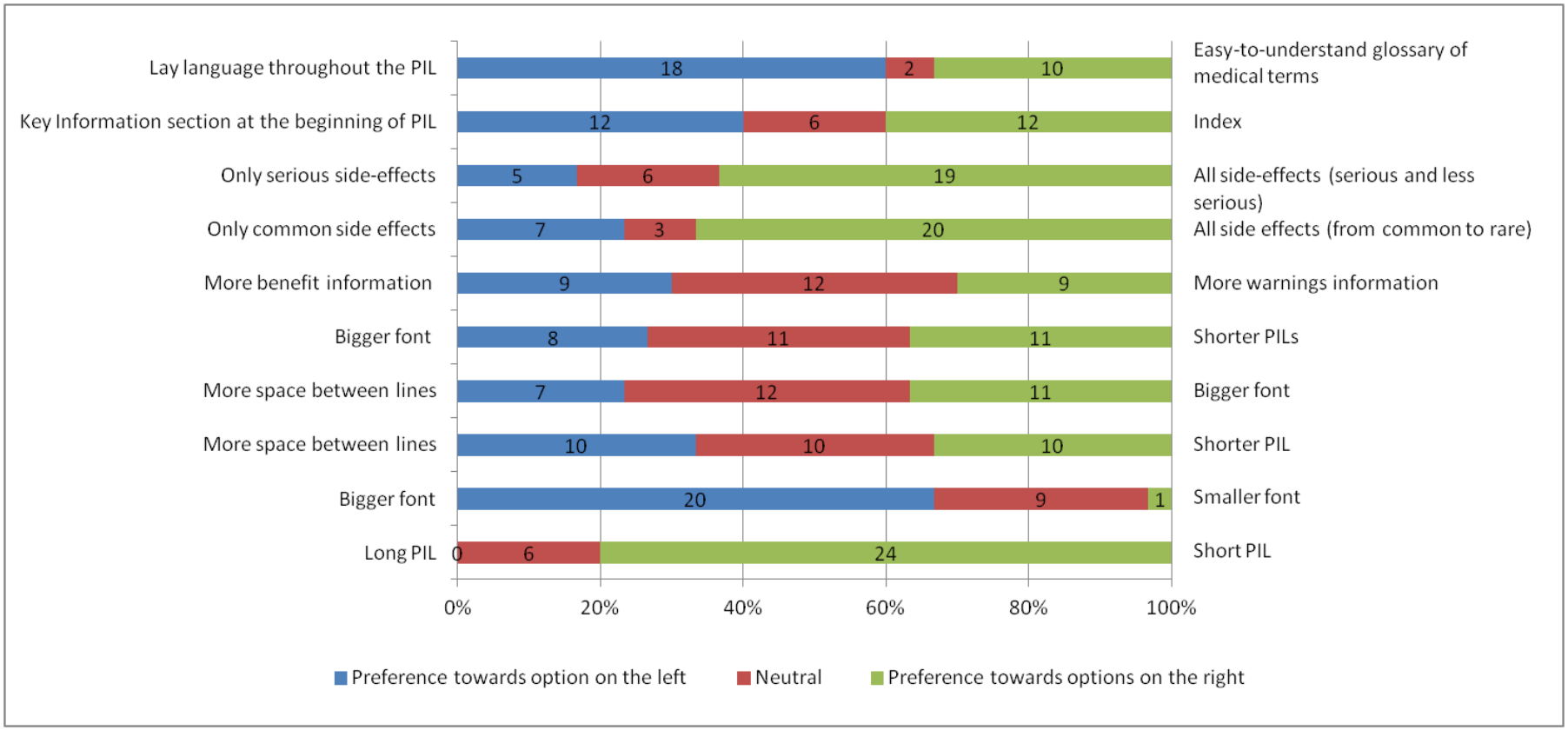


Figure 4.4– Representatives of pharmaceutical industry's preference when weighting different topics related to content and layout of PILs.

4.6.2 Sections to be included in the PIL

In order to get more grip on the question on what information is most needed in the PIL, participants were asked to select, from a list including all sections as currently included in the PIL, the 10 sections that absolutely need to be included in the PIL (follow-up questionnaire). Table 4.9 lists all the sections, in order of preference. The top 10 sections to be included in the PIL overlap to a great extent between stakeholder groups. Sections in the top 10 of all stakeholders include for example what the medicine is and what it is used for, interactions with other medication, contra-indications and use by pregnant or breast-feeding women/information on fertility.

Table 4.9 Top-10 sections to be included in the PIL according to stakeholders (follow up round)

Representatives of patient and consumer organizations (N=36)	Representatives of health care providers organizations (N=12)	Representatives of pharmaceutical industry (N=30)
1. What medicine X is and what it is used for (n=32)	1. Interaction with other medicines (n=12)	1. Contraindications (n=28)
2. Contraindications (n=28)	2. What medicine X is and what it is used for (n=11)	2. What medicine X is and what it is used for (n=26)
3. Interaction with other medicines (n=28)	3. Contraindications (n=11)	3. Use by pregnant or breast-feeding women, information on fertility (n=26)
4. Dose (n=25)	4. Use by pregnant or breast-feeding women, information on fertility (n=10)	4. Interaction with other medicines (n=24)
5. Use in children (and adolescents) (n=23)	5. Effects on the ability to drive or use machines (n=10)	5. Appropriate precautions for use and special warnings (n=21)
6. Use by pregnant or breast-feeding women, information on fertility (n=22)	6. Appropriate precautions for use and special warnings (n=9)	6. Dose (n=21)
7. Description of side effects (n=18)	7. Interactions with food and drink (n=9)	7. Use in children (and adolescents) (n=17)
8. Appropriate precautions for use and special warnings (n=16)	8. Use in children (and adolescents) (n=5)	8. Description of side effects (n=16)
9. Interactions with food and drink (n=16)	9. Excipient warnings (n=5)	9. Interactions with food and drink (n=14)
10. Effects on the ability to drive or use machines (n=15)	10. Description of side effects (n=5)	10. Storage conditions (n=13)

4.7 Summary main results

The PIL: how does it inform patients?

Patient and consumer organizations, health care professionals and user testers are sceptical about the overall quality of the PIL. Additionally, the majority of health care professionals who participated in the study think that the PIL does not include

sufficient information for the elderly and patients with more than one illness. All stakeholders agree that including more benefit information – as has tended to be done more in more recent developed PILs – may be important in improving patients' understanding of the PIL, also in order to balance the risk information. When including such benefit information there is a preference for not including numbers or estimates of risks among the different stakeholders. However, the optimum method for providing benefit information remains unclear, particularly as benefit information should not be promotional and within the limits of scientific evidence.

The PIL: problems and consequences

Results from the stakeholder consultation indicate several recognised problems with the PILs which could hamper patients' good understanding. Problems related to the content of PILs that they are too difficult (too many medical terms), there is too much text and there are too many side-effects mentioned. With regard to lay-out the small font and the length of the PIL are often mentioned. Participants mainly believe that the problems affecting understanding of the PILs are the same for elderly and low literate as for patients in general. The majority of stakeholders stated that they are aware of problems negatively affecting patients' understanding of the PIL. Consequence of these problems include, according the different stakeholders that readers are alienated from PILs and give up reading or that poor comprehensibility may result in inappropriate actions, including non-adherence to medication. Moreover, patients may be worried without good reason and may start distrusting their medicines.

The PIL: regulatory issues

To comply with EU legislation, applicants for market authorisation should follow the Quality Review of Documents (QRD) template, provided by the European Medicines Agency (EMA). The information covered in this template was judged highly relevant by patient and consumer organizations. The content of the information to be included in the QRD template is dependent on what is established in the legislation, namely article 58 of Directive 2001/83/EC. As such, the information encompassed in the QRD, either related to its content or structure, is strict and highly regulated. The majority of the representatives of all stakeholders would like to keep the QRD template regulated as it is now in terms of its content and structure (except for the pharmaceutical industry finding that the content of the QRD should be less regulated). The majority of both representatives of patient and consumer organizations and pharmaceutical industry think that OTC medicines should be regulated the same way as prescription medicines. Remarkably, a large majority of patient and consumer organizations is not aware of the requirement of patient consultation that is effective as of October 30 2005.

The PIL: trade-offs between main solutions suggested

Both in the literature and the stakeholder survey suggestions for improvement were provided, some of which are virtually impossible to combine, such as increasing the font of the text used in the PIL and, at the same time, decreasing the length of the PIL. Therefore, we asked stakeholders to make trade-offs for ten pairs of potential solutions. From these trade-offs it becomes clear that a bigger font and more spacing between the lines is preferred above having a shorter PIL by patient and consumer organizations, while HCPs have a preference for a bigger font above a shorter PIL (but not for more spacing between the line). With regard to content representatives of patient and consumer organizations prefer to have all side effects mentioned in the PIL while HCPs are inconclusive in this respect.

Chapter 5 Stakeholder survey -Summary of Product Characteristics

The Patient Information Leaflet is based upon the Summary of Product Characteristics (SmPC). The SmPC is mainly meant to be used by health care professionals who prescribe and deliver medication. In this chapter, points of views from the health care professionals as well as the pharmaceutical industry will be elaborated upon.

5.1 Methods and participants

Questions on the SmPC were asked to HCPs and pharmaceutical industry representatives. The description of how participants were recruited can be read in section 4.1.1. The response and the respondents' characteristics are described in section 4.2.
With regard to the questionnaire, it proved that not that much information was available in the literature on problems and positive points of the SmPC. Therefore, many open questions were asked. If possible questions for the PIL were adapted for the SmPC. The questionnaire was aimed at identifying possible shortcomings of the SmPC, and its consequences, as well as identifying positive points. The perceived impact of the SmPC for patient safety and rational use/prescribing of medicinal products was also investigated. Finally, respondents were asked for recommendations for improvements of SmPCs and questions concerning the European regulation of on the SmPC.

HCP representatives were not only asked to assess the content and layout of SmPCs in general but also for five particular SmPCs. The examples were the same as those for the Patient Information Leaflet: an over-the-counter medicine (medicine A, authorised after 2005), a bisphophonate (medicine B, authorised after 2005), a medicine for respiratory complaints (medicine C, authorised before 2005), a antihypertensive (medicine D, generic, authorised before 2005) and an antibiotic (medicine E; authorised before 2005).[20] Since five examples would originate very long questionnaires, it was decided to randomly divide respondents in two groups and each of the groups analysed three SmPCs. Group A analysed medicines A to C and group B analysed medicines C to D. As measurements were rather similar to those of the PIL, they will not be described here. If needed , they will be explained in the relevant results section. To analyse the data we mainly used descriptive analyses (frequencies, cross tabulation, means). Additionally, in case we wanted to calculate sum scores for a series of items, we calculated the reliability for doing so using Cronbach's alpha.

[20] Decision made after consultation with EMA.

5.2 Use, judgement of content & layout of SmPCs

5.2.1 When to consult the SmPC?

Representatives of health care providers organizations (N=28) were asked their opinion on the use of SmPCs. In HCP representatives' opinion, the need to access the SmPC exists when a HCP needs to know more about a new medicine (82.8%), contraindications (75.9%), interactions with other medicines (72.4%), therapeutic indications (69.0%), dosing and method of administration (69.0%), special warnings and precautions of use (69.0%), side effects (69.0%), and a medicine not frequently prescribed or dispensed (62.1%).

5.2.2 Judgement on content, layout and overall quality

Overall quality

HCPs were asked to rate the content, layout and overall quality of SmPCs, on a scale from 1 "low quality" to 9 "high quality". [21],[22] Participants rated the overall quality of SmPCs with a mean score of 6.5 (CI 5.8 and 7.2), which is higher compared to the PIL.

Content

With regard to the content, specific questions were asked with regard to the ease of finding information, the length of the text, the use of short sentences, the ease of understanding words and the use of familiar terms. When asked for SmPCs in general, scores were largely comparable, with the exception of *use of short sentences* receiving a lower score (Figure 5.1.a). Overall, SmPCs in general received a mean (sum)score of 6.0 (CI 5.3-6.6; α (scale) = 0.83) in terms of content. Figure 5.1 also provides the scores for the five examples. The overall picture is largely comparable.

Layout

Specific elements of the lay-out of SmPCs such as font size, use of pictograms, and use of bolt were also asked for both for SmPCs in general and for the five examples. Scores were rather similar for all elements (Figure 5.1.b). Also, there were no clear differences between the judgement of the SmPC in general and the five examples. Overall, SmPCs received a mean score of 5.9 (CI 5.3 and 6.5; α (scale) = 0.92).

[21] Note that all SmPCs examples were assess online, by using a link given in the questionnaire.
[22] The number of participants who assessed the examples of SmPCs was smaller than the ones assessing the SmPC in general.

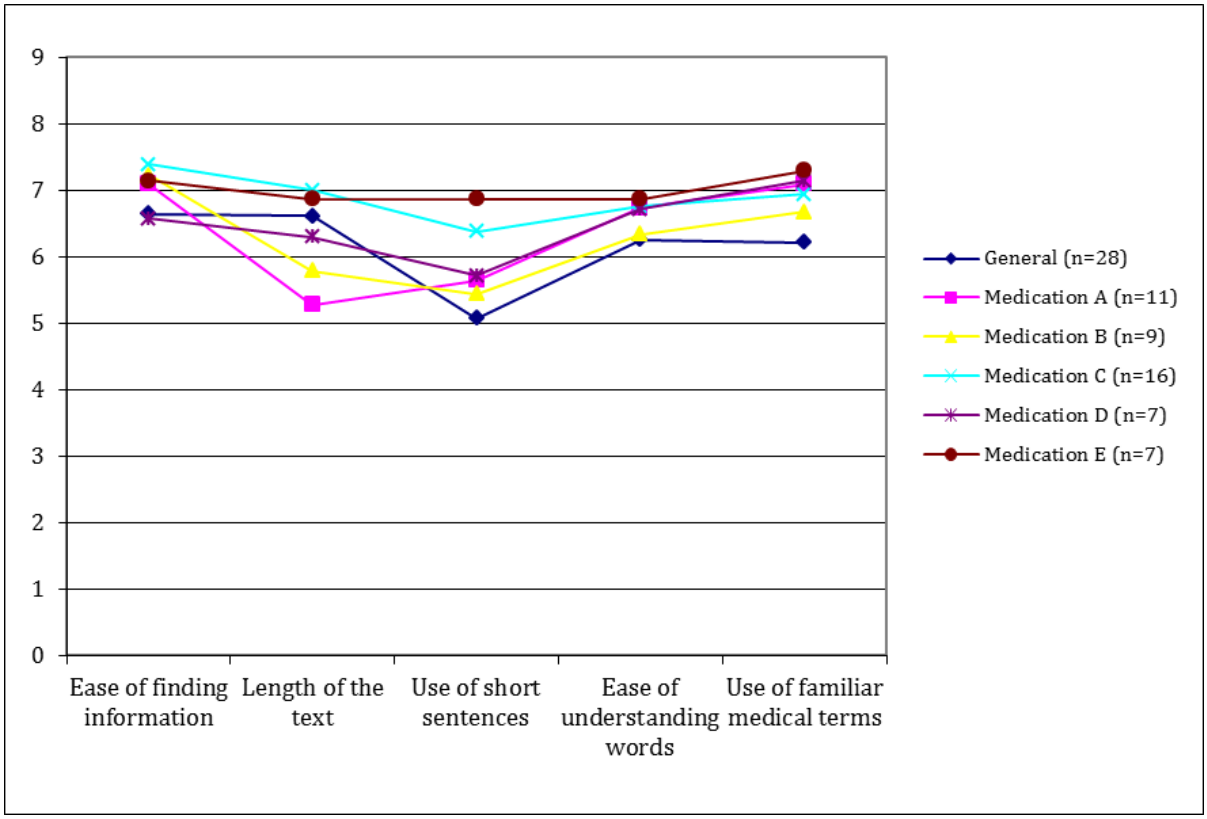


Figure 5.1.a – Assessment of content of SmPCs by health care providers organizations.

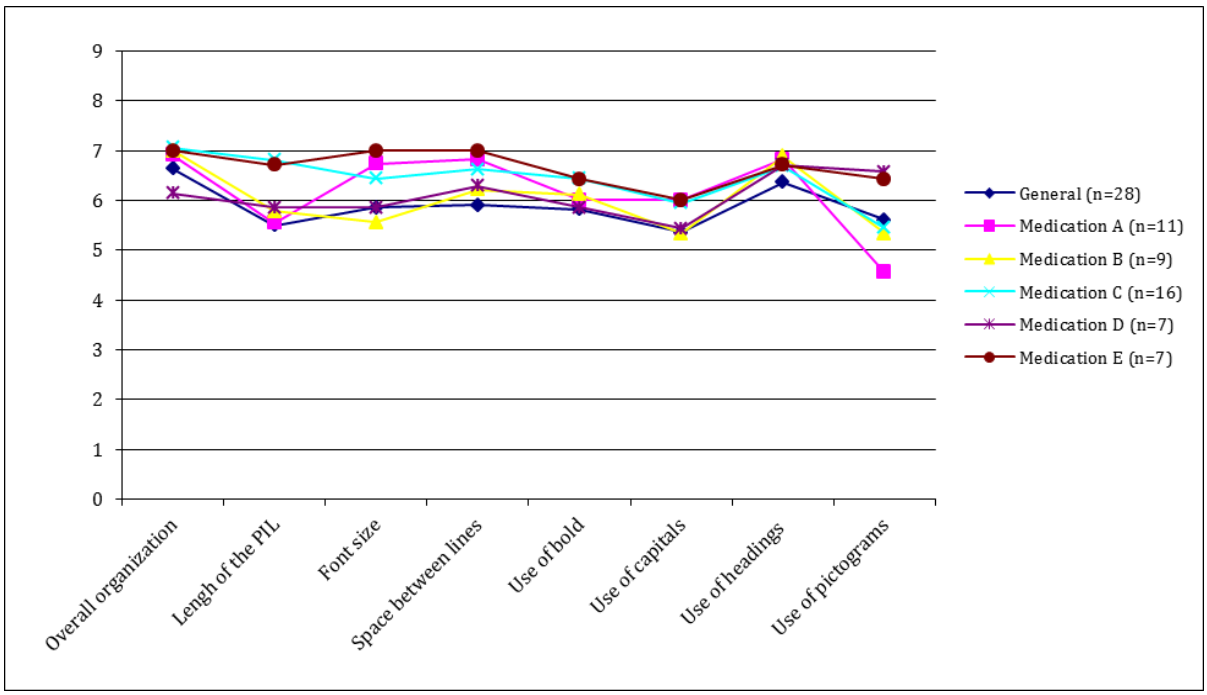


Figure 5.1.b– Assessment of layout of SmPCs by health care providers organizations.

5.2.3 Current content of the SmPC

Assessment of importance of sections included in the SmPC

We asked respondents how important they considered the different sections included in the SmPC. Both representatives of HCPs and pharmaceutical industry organizations rated the sections currently included in the SmPC as fairly important (Figure 5.2). Both stakeholder groups found preclinical safety data the least important to include (mean values of 6.2 and 6.5, respectively). Sections that are rated 8 to 9 on average among both stakeholders include name of the product, undesirable effects, pregnancy and lactation, interactions with other medicinal products, special warnings and precautions of use, instructions for use, posology and method of administration, and therapeutic indications.

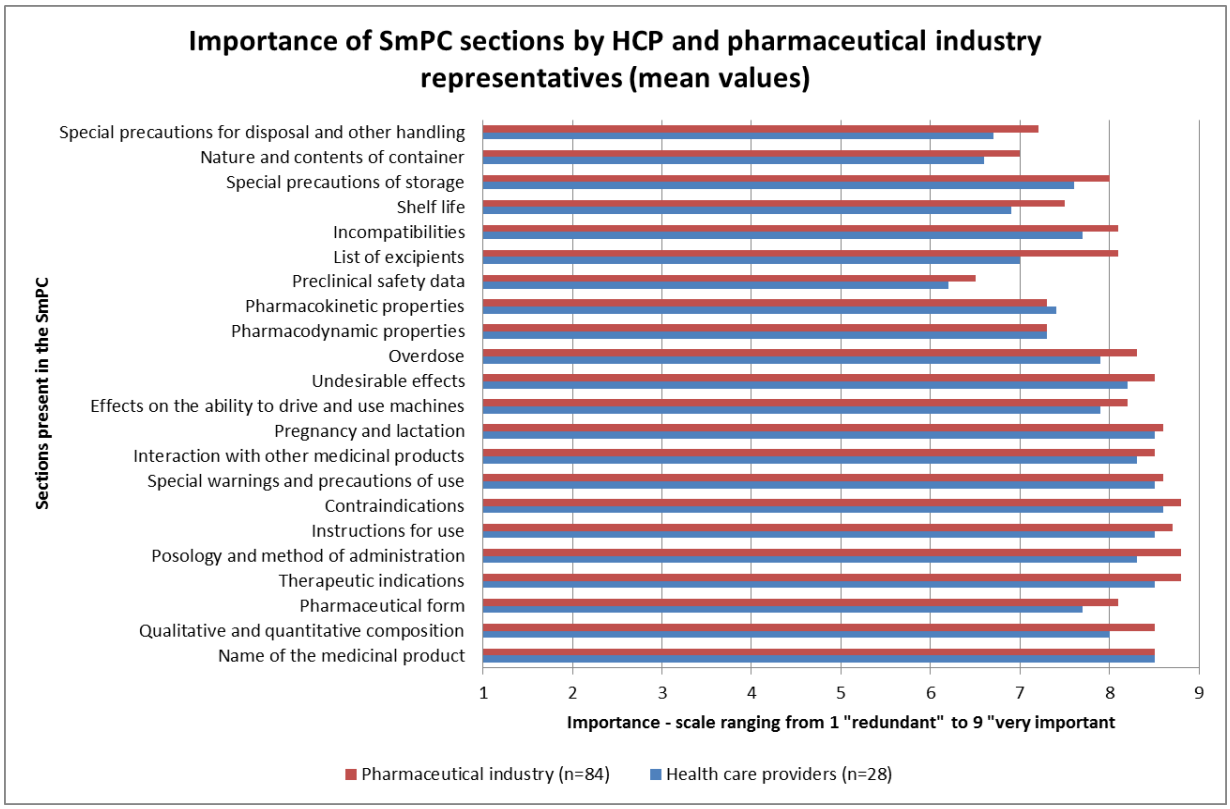


Figure 5.2– Assessment of importance of different sections currently part of the SmPC by HCP and pharmaceutical industry representatives.

Does content fits needs for specific target groups?

According to the majority of HCPs (N=28) and pharmaceutical industry (N=83) representatives, the current content of the SmPC includes sufficient information to make rational decisions while prescribing or dispensing medicines to the following specific target groups, namely, elderly (82.1% HCP; 84.3% pharmaceutical industry), patients with more than one illness (71.4% HCP; 79.5% pharmaceutical industry), pregnant women (82.1% HCP; 90.4% pharmaceutical industry), children (82.1% HCP; 75.9% pharmaceutical industry), infants (67.9 HCP; 73.5% pharmaceutical industry), and patients with long-term illness (67.9% HCP; 71.1% pharmaceutical industry).

However, concerning children and infants, participants felt that information was missing, especially regarding dosages per weight and/or age and data on studies performed in this age population. As for information currently missing for other target groups, some representatives of pharmaceutical industry organizations felt that a better distinction between gender (male/female) could be done, whenever applicable.
In general terms, the majority of the participants believed that the SmPC encompasses sufficient information which would allow HCPs to get acquainted with a new medicine (92.6% HCP; 80.7% pharm. industry) and to answer specific questions for specific groups of patients (66.7% HCP; 68.3% pharmaceutical industry).

5.2.4 Highlighting information in the SmPC

The way important information can be highlighted in SmPCs was judged slight differently by HCPs and pharmaceutical industry representatives. For HCP representatives (N=22) the use of bold (72.7%) was the preferred way, followed by the use of bigger font (54.6%), use of boxes (36.4%) and, lastly, the use of different colours (31.8%). As for pharmaceutical industry representatives (N=83), the use of bold was also the preferred way to highlight important information (50.6%), followed by the use of boxes (36.1%), use of bigger font (21.7%), and use of different text colors (14.5%). Other methods were suggested by participants, namely a "better structure of the SmPC" (7.2%), "use of headlines including key messages" (2.4%), "use of bullet points" (2.4%), and "underline important text" (2.4%). However, 15.7% of the representatives of pharmaceutical organizations mentioned that the information on the SmPC does not need to be highlighted since all information is important and relevant for health care professionals.

5.3 Perceived problems & consequences and positive points of the SmPC

5.3.1 Perceived problems & consequences of the SmPC

Representatives of health care providers' organizations and pharmaceutical industry were asked to give input on problems negatively influencing the understanding of SmPCs

Representatives of HCP organizations

The majority of the respondents was not aware of factors which could negatively influence the understanding of SmPCs (16 out of 22; 72.2%). The remaining respondents (6 out of 22; 27.2%) were aware of some problems. In total, 10 factors were mentioned by these respondents which varied from the age of the HCP to the extensive length of the SmPC to , the duality of information.
The following solutions to overcome the problems mentioned above were given by participants such as: "shorter and more concise SmPCs", "involvement of pharmacists in the development of the SmPCs as part of the license and marketing requirements", and "quicker updates".

Representatives of pharmaceutical industry

Almost one third (29%; n= 83) of the representatives of the pharmaceutical industry mentioned factors that may have a negative impact on the understanding of the SmPC; 28.9% was not aware of any negative factor influencing the understanding of the SmPCs and 36.1% did not know of any factors.

According to representatives of pharmaceutical industry, the following problems were enumerated (by at least 2 participants):

- the information included in some sections (e.g. indication, posology, pharmacological properties) is too extensive (n=7)
- too much emphasis on regulatory aspects which are not relevant for the HCP (n=5),
- information presented in the SmPC does not allow the physician to make a benefit-risk assessment for an individual patient (n=2)
- use of too long sentences (n=2)
- SmPCs are too long (n=2),
- bad quality of translations to local languages (n=2)

As far as solutions to overcome the problems mentioned are concerned, these were vary varied but referred to more clear layout (for example bullet pints, use of headlines) and to reducing the amount of information by being more concise and avoid repetition.

5.3.2 Positive points of the SmPC

Both representatives of HCP organizations and pharmaceutical industry were asked about aspects that facilitate the correct understanding of SmPCs. Four out of 22 respondents pointed out aspects that positively influence the understanding of SmPCs. About one third (30%; 26 out of 83) of the representatives of the pharmaceutical industry knew factors that positively influence the understanding of the SmPC, which was the same percentage of participants not being aware of any positive point (30%; 26 out of 83); 31 out of 83 (37.4%) representatives did not know of any factors. Factors mentioned were varied and no clear picture emerged.

5.4 Regulatory questions on the SmPC

In order to obtain a marketing authorisation for a medicinal product, applicants must include a Summary of Product Characteristics (SmPC) in accordance with Article 11 of Directive 2001/83/EC (see Chapter 2 for a description of this article). For the full information to be included in each section of the SmPC, applicants should refer to the "Guideline on Summary of Product Characteristics".
(http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).

Only half of the representatives of HPC organizations (14 out of 27; 51.9%) were familiar with this European guideline (question not asked to representatives of pharmaceutical industry). For answering further questions HCPs were provided with a link to this guideline. The guideline was rated as (very) important by the majority of representatives of HCP organizations (20 out of 27; 70.1%) and pharmaceutical industry (76 out of 82; 92.7%). A quarter of the (7 out of 27, 25.9%) representatives of HCP organizations had no opinion regarding the guideline, against 6% (5 out of 82) representatives of pharmaceutical industry.

We asked whether participants would prefer this guideline to regulate more or less the content and the structure (i.e. the order of the sections as currently presented) of SmPCs. Half (51.9%) of the representatives of the HCPs and about two third (68.3%) of the representatives of the pharmaceutical industry think that the requirements regarding the content of the SmPC should stay as they are. For the structure these percentages are even higher (59.3% and 77.2% respectively). A large group of HCP representatives had no opinion as to whether or not to change the regulation on

content and structure of the SmPC. Those HCP representatives who want a change are more in favour of more regulation. This is contrary to the pharmaceutical industry representatives who want a change: they more often prefer less regulation in order to create more flexibility.

Table 5.2 – Content and structure of SmPCs – should it be more or less regulated?

		Representatives of health care providers organizations (N=27)	Representatives of pharmaceutical industry (N=82)
Content of EU guideline	More regulated	2; 7.4%	3; 3.7%
	Less regulated	1; 3.7%	14; 17.1%
	The same	14; 51.9%	56; 68.3%
	No opinion	10; 37.0%	9; 11.0%
Structure of EU guideline	More regulated	2; 7.4%	0
	Less regulated	0	8; 10.1% *
	The same	16; 59.3%	61;77.2% *
	No opinion	9; 33.3%	10; 12.7% *
	* Total number of participants, N=79.		

Respondents who wanted a change were asked why and what kind of change they wanted. Regarding the content of the European guideline, participants preferred a more regulated guideline since in it would allow more standardization of the information (n=2 HCP; n=2 pharmaceutical industry). On the other hand, less regulation towards content would enable more flexibility and tailoring (n=4) ("*not all medicines are absolutely equal"; "it depends on the medicine and what a user needs to know about it; the template makes 'different types of use' very difficult."* – example of some quotes of pharmaceutical industry representatives).

As far as the structure of the guideline is concerned, the majority of representatives preferred it to be regulated the same way as currently is. However, two representatives of HCP organizations preferred to have the guideline more regulated for standardization sake. Representatives of pharmaceutical organizations, on the other hand, would like this guideline to be less regulated in terms of its structure, allowing for more flexibility, for example: "not all medicines are the same. Information about them needs to follow a structure that is relevant to the reader. At the moment, that is not possible".
Representatives of HCP organizations (N=27) and pharmaceutical industry (N=79) felt that the current SmPCs miss some sections while other sections could be excluded. Table 5.3 summarises those sections. Yet, only a few respondents mentioned one of those sections.

Table 5.3 – Summary of SmPC sections that representatives felt were missing or should be excluded.

	Representatives of health care providers organizations (N=27)	Representatives of pharmaceutical industry (N=79)
Sections currently missing according to 14.8% (n=4) of HCP organizations' representatives and 8.9% (n=7) of representatives of pharmaceutical industry.	Special consideration for specific patient groups (n=2). Dosing in the elderly*. Side effects/contraindications for people with chronic illness. Pediatrics and off-label.	Benefit section (n=3). Guide for communication with the patient. Information regarding infants.
Sections that could be excluded according to 11.1% (n=3) of HCP organizations' representatives and 10.1% (n=8) of representatives of pharmaceutical industry.	Section 6 - Pharmaceutical particulars Section 7 - Marketing authorisation holder. Section 8 - Marketing authorisation number(s). Section 9 - Date of first authorisation / renewal of the authorisation (n=2). Section 10 – Date of revision of the text. Some information could be simplified and combined, as follows: • Special section about Driving included in the warning section • Special section about pregnancy and lactation included in warning section.	Section 5 – pharmacological properties – not really excluded but shortened and/or simplified. Compress the volume of sections 5 to 12. Information on overdose - could be provided as separate information since this patients are normally seen in the hospital. Shelf-life (part of section 6, pharmaceutical particulars). Section 8 - Marketing authorisation number(s). Section 9 - Date of first authorisation / renewal of the authorisation (n=2) Section 10 – Date of revision of the text.

*) if no number of participants is mentioned in the table, there was one participant who missed or wanted to delete the section mentioned

5.5 Summary main results

The SmPC: how does it inform professionals

Health care providers are generally positive about the content and layout of SmPCs. Sections that were considered highly relevant to be included in the SmPC were, according to HCPs: name of the product, undesirable effects, pregnancy and lactation, interactions with other medicinal products, special warnings and precautions of use, instructions for use, posology and method of administration, and therapeutic indications. The majority of the HCPs think that SmPC includes sufficient information to make rational decisions while prescribing or dispensing medicines to the specific target groups such as the elderly, patients with more than one illness, pregnant women, and patients with long-term illness. Concerning children and infants, participants felt that information was missing, especially regarding dosages per weight and/or age and data on studies performed in this age population. However, such information may not be known and hence cannot be included.[23]

The SmPC: problems and consequences

The majority of the HCP representatives was not aware of factors which could negatively influence the understanding of SmPCs. Almost one third of the representatives of the pharmaceutical industry mentioned factors that may have a negative impact on the understanding of the SmPC. Problems most frequently mentioned were that information in some sections is too extensive and too much emphasis on regulatory aspects which are not relevant for the HCPs.

The SmPC: regulatory issues

In order to obtain a marketing authorisation for a medicinal product, applicants must include a Summary of Product Characteristics (SmPC) in accordance with Article 11 of Directive 2001/83/EC. For the full information to be included in each section of the SmPC, applicants should refer to the "Guideline on Summary of Product Characteristics". Only half of the representatives of HPC organizations were familiar with this guideline. The guideline is considered to be important by the majority of representatives of HCP organizations and pharmaceutical industry. Half of the representatives of the HCPs and about two third of the representatives of the pharmaceutical industry think that the requirements regarding the content of the SmPC should stay as they are and for the structure these percentages are even higher.

[23] See for example"Ivanovska V, Mantel AK, Van Dijk L. Background Paper 7.1. Priority Medicines for Children. In: Laing R.O et al (eds) Priority Medicines for Europe and the World. A Public Health Approach to Innovation". 2013. (http://www.who.int/medicines/areas/priority_medicines/BP7_1Children.pdf)

6. Online discussion forum

Both the literature study and the online structured consultations provided insight into problems with the SmPC and much more so with the PIL. Moreover, solutions to overcome these problems were explored. These were used as the input for the last stage of the study: an online discussion forum with as its main purpose to go into more detail into potential solutions to improve the PIL. As problems with the SmPC were much less frequently reported and experienced, we decided to focus on the PIL in the online discussions. The discussion forum was opened during the second half of May 2013. We should notice upfront that the online discussion was not meant to quantify opinions but to show the solutions interested stakeholders come up with and the variety in these solutions.

6.1 Method

6.1.1 Participants

A total of 57 potential participants were approached through email. They were persons who also participated in the online survey, who helped us during the process of recruiting participants for the online survey or whose name was provided by one of the participating organizations/respondents in the survey. Of those 57 persons, 20 persons agreed to participate (Table 6.1) and 10 indeed very actively participated. Two online discussion forums were organised. One for the representatives of the pharmaceutical industry and one for all other stakeholders. The reason for doing so was pharmaceutical industry representatives may have a different interest in the topic compared to other parties.

Table 6.1 Response to the online forum discussion

Type of organization	Number approached	Number participating
Patient and consumer organizations and organizations for the elderly	10	2
Organizations of health care professionals (pharmacists and physicians)	10	3
Representatives of regulatory offices	10	4
Experts on communication in the PIL	10	6
Pharmaceutical industry	17	5

6.1.2 Method of online discussions

Online discussions have been introduced as an alternative method (compared to traditional focus group discussions) in qualitative research (69). We chose the so-called asynchronous mode of the mediated online discussion method This means that experts were be able to log in any time during a two week period. They could read each other's contributions and post own contributions and reactions whenever this was convenient for them. Researchers asked questions if needed.

The main goal of the online mediated discussion was to derive recommendations for improvement of PIL. There were five topics organised around the shortcomings of the PIL. During the first week the forum was opened, the participants daily received an e-mail to ask them to (re-)join the discussion. Each day one or two new topics were posted on the website (Table 6.2). In these topics we asked for potential recommendations as well as to discuss their relevance and feasibility as well as their value for health care professionals or patients/the general public, their contribution to rational use and to patient safety. The last day of the first week, the results from the four first days were summarised in a three-page document. Participants were asked to reflect on the summary and to add additional comments. The second week, participants could comment on all topics if they wanted but no new topics were added.

Table 6.2 Topics the online forum discussion

Day	Topic(s)
1	Lay-out related problems: volume of the text and length of the PIL
	Lay-out related problems: font size
2	Lay-out related problems: visual design/layout
3	Content-related problems: wording and understanding
	Content-related problems: Warnings and side-effects
4	How to communicate important information: highlight important information
	How to communicate important information: key information section
5	Summary

6.3 Results

In the result section, we state which stakeholder has provided the arguments described. Table 6.3. shows the abbreviations used in the text.

Table 6.3 Abbreviations used for different stakeholders

Abbreviation	Stakeholder
CE	Communication expert
HCP	Health care professional
PI	Pharmaceutical industry
PO	Patient organization
RO	Regulatory officer

6.3.1 Legislation and QRD

Respondents from different backgrounds (regulatory officers, pharmaceutical industry and communication experts) noted that the legislation hampers the readability of the patient information leaflet. A regulatory officer (RO) stated that the leaflet is dictated by the prescriptive nature of the legislation and the large number of things which need to be communicated. Amending the legislation to reduce the amount of detail required would help as well as withdrawal of the readability guideline and the QRD as they are not helpful in drawing up a leaflet. Another respondent (communication expert CE) argues that the QRD template needs to be modified. This respondents argues that "there are conflicts between the obligatory words in the template and the requirement of the amended article 63, paragraph 2 (EU-Directive 2004/27/EC amending 2001/83/EC). The Directive requires that 'Package leaflets must be written and designed to be clear and understandable, enabling the users to act

appropriately'. The texts in the QRD template do not always 'enable users to act appropriately'" (see example in Box 6.1).

Box 6.1: Example provided by a participant (communication expert) on conflicts between legislation and QRD template

> The Directive asks for information 'for the identification of the medicinal product'. According to article 63, the information must 'enable patients to identify a medicinal product'. The QRD template puts this information in 3 different places (second line in the template, section 1, and section 6). The template adds about 150 words in between the first and the second information about identification. This does not make it easy for patients to identify their medicines. Patients identify their medicines by a range of characteristics, such as their colour, their shape, their packaging. This information is provided in section 6. There is not a single method that suits all medicines. One thing that would help - for some medicines, not for all - is to add an illustration or photograph of tablets on the leaflet. This will enable some patients to identification some medicines.

The same respondent (CE) argues that the legislation should be modified: "The information that is required in EU-Directive 2004/27 is very substantial. For some medicines, in some situations, it might be possible to reduce the length by grouping information together that is now separated". This communication expert states that a more radical change would be: "to move away from a 'prescriptive legislation' (you must tell users this, this and this), to a 'performance based legislation' (you must 'enable users to act appropriately'). The current legislation and guidelines are somewhere in between" . This experts adds that the readability tests frequently show that the order of information, nor the standard phrases, are optimal for specific medicines in specific circumstances". A regulatory officer (RO) states that legislation should also address the principles of good information design. A pharmaceutical industry representative (PI) adds that competent authorities should not substitute personal opinions or preferences for information that has successfully undergone rigorous user testing.

6.3.2 Length of the PIL

It has been mentioned in the scientific literature that PILs may contain an excessive amount of information. In order to fit all mandatory and necessary information, PILs became (too) long. The idea is that both the volume of information and the extensive size of PILs discourage patients from reading it until the end. Results from our survey supported these findings. We asked the respondents for possibilities to decrease the length of the PIL.

Several options have been mentioned in order to reduce the length of the PIL. As one respondent mentioned: "There are several factors that increase the length of the text in a PIL. There are several ways to modify leaflets to make them shorter, and it is likely that a combination of these modifications will be most effective. It is probably necessary to provide a range of options" (CE).

Information that can be excluded from the PIL

First, length reduction can be achieved by skipping information from the PIL. Most frequently mentioned here is the exhaustive information on all marketing authorisation holders in the EU (mentioned by respondents with different backgrounds). Other topics mentioned include pack sizes (RO, PI 2x), dosing and content declaration (PI). A pharmaceutical industry representative argues that a lot of specific information on when to contact your physician could be mentioned in shorter, general terms, stressing the importance to keep contact with the physician (PI). Furthermore, there is debate as to how to address side effects. A regulatory officer stated that long lists of side effects are frequently criticised as being off-putting and that the legislation should consider how best to address this. A HCP representative wondered whether the frequency of the potential side effects could decide: "Maybe only the frequent ones could be mentioned, and the others could be designated as for example; "all other detected side effects were extremely rare." (HCP) A pharmaceutical industry representative agrees upon this (PI). The problem of repeated information at different places in the PIL was mentioned by several stakeholders as well. By avoiding such repetition, the length of the PIL can be shortened.

Changing design, order and layout

Second, design and lay-out related arguments were posed, albeit a communication expert stated: "Changing the layout/design does not really help because this will not make the text shorter"(CE). Yet, other participants stated that the visual length can be reduced by changing the design for example by using landscape instead of portrait paper (RO; PI) as it can be beneficial in making the information appear less dense and in a larger text size (RO). Also font choice was mentioned (PI). This last respondent also proposed an alternative format e.g. booklet form with pages/sections for the different key messages, that in case they are not feasible to fit in the pack could be made available by the pharmacists at the point of sale. Other lay-out related issues include the use of bullets and shorter sentences (PI).

Electronic version and paper versions

The issues of a combined use of electronic information and information on paper was mentioned by all types of stakeholders. Most of them suggested to put the most relevant information that patients need to know in the paper version of the PIL and then to refer with web links to other relevant information (RO, PI, CE). This should then become a mandatory requirement (PI). A text such as the following could be added: "This leaflet cannot tell you all the information about this medicine. Your pharmacist can help you to find this, and you can find it yourself at: www.medicinename.rx or www.ema.europe.eu" (CE) What 'most important' information is may depend on the medicine which allows for more flexibility also to tailor the information more towards individual patients. For example, a first-time user would be interested in different information than a user who is already familiar with the product. (PI). Using electronic sources would enable information to be accessed in a variety of formats e.g. XML files as well as in different languages if websites include translation options. This would enable PILs to become shorter focusing on essential information only and cutting out duplicated information and packaging to be optimised (PI).Electronic dissemination of product information could also help to navigate easier through the information. It allows to provide searchable, up-to-date and customised information. (PI).

6.3.3 Font size and line spacing

The European guideline on the readability of the labelling and package leaflet of medicinal products for human use recommends to type PILs with: "a font which is easy to read. (…) A type size of 9 points, as measured in font "Times New Roman", not narrowed, with a space between lines of at least 3 mm, should be considered as minimum". Despite clear guidance and recommendations, results from our stakeholder consultation (chapter 4) showed that the majority of respondents think that a "font size too small makes the PIL hard to read". Additionally, representatives of patient organizations seem to prefer a bigger font size and more space between the lines over shorter PILs. We asked the participants in the online discussion for their opinion.

Font size

The guidelines concerning the font size are criticized by different stakeholders (RO, PO, HCP, PI). There is very little, if any, evidence that Times New Roman 9 point could be used as a standard for 'readable texts (CE). The currently used font sizes seem to be a compromise between readability and length of the texts (PI) and reducing the volume of information required will enable companies to use larger font sizes more of the time (PI). A patient organization representative stated that "Times New roman is not the more age-friendly font. Arial font is much clearer and easier to read already from size 9" (PO). A regulatory officer adds that the readability guideline recommends a font size which is too small for many readers and argues that it would not pass the requirement of article 63 in Directive 2001/83/EC: to be clear and easy to read. This participant adds that: "with all this being specified in guidance is that often that is all that the applicant company will use". (RO). A potential solution is, according to this participant, to move away from paper towards electronic access although not all citizens have access to electronic media. Yet, electronic dissemination would allow patients to customise the text to their individual need (bigger font or audio files) (PI).

A communication expert states that the font (or point) size "is a vertical dimension of type originating from old printing technology. Point sizes are still used in current software but their practical relevance is very small". Moreover, according to this participant, it is impossible to determine the vertical dimension of the printed characters in point sizes after a text has been printed and can be seen on paper. This expert suggests to use the x-height (the vertical dimension of a lower case 'x') instead as suggested in the new German DIN-standard (introduced in April 2013) that states that a minimal x-height must be 1,50 mm (CE#8). The vertical dimension of the lower case x of Times New Roman, recommended in the Readability guideline is around 1,422 mm (CE).

Line spacing

Clear spacing between lines is wished for. A patient organization representative (PO) refers to the Canadian 'Clear Print Guidelines'[24]. A communication expert criticises the Readability Guideline which states that 'Line spaces should be kept clear': it is not clear what is meant by this statement. This participant (CE) also discusses Section 1 of the Readability guideline where it states that 'a space between lines of at least 3 mm' should be considered for three reasons:

1. There is no evidence that this dimension leads to 'more readable texts';

[24] http://webcache.googleusercontent.com/search?q=cache:3xVjlFLfxOkJ:www.cnib.ca/en/services/resources/Clearprint/Documents/CNIB%2520Clear%2520Print%2520Guide.pdf+&cd=3&hl=nl&ct=clnk&gl=nl

2. It is unclear which vertical dimension is exactly meant (baseline to baseline?, baseline to top x-height?, baseline to top capitals?);
3. It is in conflict with the advice that is given in section 2: line space should be 1.5 times the word space.

A broader view

A regulatory officer argues that focusing on the font and text size may be too narrow a perspective and a "bigger picture" view should be considered (RO). For example the principles of good information design are not covered in the current legislation. This could deal with many of the issues noted by patients but would also likely result in longer leaflets which in themselves will be off-putting. This broader view is supported by a communication expert who states: "the typographical specification of text is a fairly complex activity that needs skills and experience. It is not something that can be put into 'simple and straightforward standard rules'. It is not only the specification of the main text, but also the consideration of the design of the headings, columns, lists, tables, diagrams, illustrations, pictograms, in different languages, that needs to be considered simultaneously" (CE). This expert pleas for providing a number of visual examples that could be followed.

User testing

A communication expert (CE) states that it is obligatory to test a PIL with at least 20 people. If the type size is too small, it will not pass a readability test. Hard rules on typography are not important as long as a user test shows that patients can read a package leaflet comfortably. This participant, however, puts some question marks with regard to current readability tests as they are – to his opinion - not optimally suited to check and confirm whether or not a text is really 'readable'.

The conclusion is that from a communication point of view, legislation and readability guidelines should be improved in terms of typography, especially for the main texts that must be read by patients for safe and appropriate use. Yet, too strict rules may be counter-productive.

6.3.4 Design & Content (in light of legislation & guidelines)

We asked participants to the online discussion how the design of the PIL can be improved. Design is a critical factor in getting patients to read the information so it needs to be addressed, as a regulator officer stated (RO).

Several pharmaceutical industry representatives state that considerable progress has been made in this area over the last years (PI# 5x) as a result of user testing (PI). User testing is recognised as good instrument to improve PILs. Yet, all stakeholders they think (further) improvements can be made. Different stakeholders stated that design and content of the PIL should always be considered simultaneously as they support each other (PI, CE, RO). The content of a PIL should not be dissociated from its layout/design. Moreover, several aspects of design need to be considered jointly. A HCP representative pleas for the "kiss" communication (keep it simple and short) and argues that an attractive and clear design with emphasised bold text can definitely improve the comprehensiveness of information (HCP).

As stated before, a recommendation put forward is to address "information design"[25] in the current legislation (RO). One of the pharmaceutical industry representatives states that companies are already taking account of the broad principles of information design regarding use of white space, sectioning, bulleted lists, text alignment etc (PI).

Another recommendation is that EMA and national regulatory agencies could publish PILs as examples of good practice, making it easier for the industry to follow the good examples. In the UK, the MHRA has put this in practice (PI). One participant signals that, although it is a good idea, there may be a risk to this as well namely that the format of the examples would be too easily copied without thinking about optimization of the information for that specific medicine (RO). Another participant adds that the MHRA website only provides the "end results" of the good examples, but it would be even more useful to share the information development process of good examples (CE). According to the participants, best practice should be promoted much more. Also, users should be more involved in the process by user testing. A communication expert proposes to introduce an iterative process of writing - designing - testing that leads to PILs that really 'enable users to act appropriately'. Separating the activities of writing-designing-testing does not lead to satisfactory results. Current PILs, the QRD-template, and the Readability guideline itself show the consequences if these activities are treated separately (CE). Such process should also be adopted for the development of guidelines.

While some participants think the current legislation functions satisfactory, the application of legislation is not adequate according to some other participants. They mention that the current European guideline is not clear enough and provides imprecise advice (CE), does not include information design (RO) and is inflexible with regard to individual needs (RO; PI). Yet another participant pleas for standardization in legislation as it is now (RO). A pharmaceutical industry representative states that in order to encourage innovation and improvement it would not be desirable to over-legislate in this area but instead allow for flexibility and continue to improve on best practice sharing (PI). According to this participant, the role of the Commission and regulators should be limited to raising awareness of the discipline and providing examples of good medicines information design. Another pharmaceutical industry representative argues that the results of user testing are paramount and should take precedence over national guidelines or assessors' recommendations (PI).

Finally, also with regard to the design, the value of electronic formats is mentioned, for example to further improve the attractiveness for readers with modern habits or with special needs such as blind or visually impaired patients (PI, 3x). This last group could be helped by offering the possibility of bigger font sizes or audio files. The paper leaflet in the package is much more bound by technical aspects than new technical solutions. A pharmaceutical industry representative states: "It is not possible to meet the individual needs of specific sub-groups in a 'generic' PIL accompanying the medicine; these can be better addressed using electronic solutions" (PI). A regulatory officer adds that there is much to recommend only the key points being included in the paper version with more detail being provided in an on-line version. (RO). Yet, this participant adds: "This would mean of course that healthcare professionals would need to spend more time going through the detail with patients and this would require a culture change".

[25] This is the practice of presenting information in a way that fosters efficient and effective understanding of it.

6.3.5 Comprehensibility-related problems

Participants in the online discussion argue that it is not possible that a single leaflet provides "everything for everyone at all times" (CE) and state that the PIL is "a classic one size doesn't fit all (RO). A regulatory officer states that the PIL is intended to give general basic information that is applicable to and understandable for most of the patients (RO). Participants agree that to reach to goal of " acting appropriately", there should be a combination of information provided by the health care providers which needs to be supported by the PIL accordingly.

A communication expert adds that the total amount of information patients receive (for example when they receive three medicines together) is too confusing to handle, even for highly educated and skilled readers. The participants stress the role of the HCPs to support patients in this (RO 2x, CE) as a package insert cannot solve all these different problems. It can only emphasise the main points and provide instructions where to ask for more support (CE). Another problem brought up is that the text in the PIL seems to come from different sources: patients are referred to their doctor or pharmacist, to the Marketing Authorisation Holder, to the EMA-website, and sometimes to patient organisations. It does not 'speak with one voice' and this confuses patients. A regulatory officer (RO) pleas for doctors or pharmacists to be the gatekeepers of the information provided to patients; this would be the ideal rather than the company. The PIL needs to support the doctor and pharmacist so there needs to be a more joined up approach to information provision. A communication expert (CE) agrees on this and puts forward the following considerations:

- relate the contents of a PIL to the contexts/situations in which a medicine is used.
- support and stimulate the dialogue between patients and healthcare providers.
- are reliable and trustworthy to enhance the confidence in the quality of the information.

For all three, it is essential to start from a dialogue with patients about their medicines. The current combination of European legislation, QRD-templates, and guidelines can prevent this dialogue taking place (CE).

The same expert argues that in case of new regulations and new guidelines it is important to make a very diverse range of PILs possible. Another problem mentioned is that the PIL is tied to the pharmaceutical company which hinders the production of consistent and sensible information about medicines. Lack of consistency is a common problem and this is going to be difficult to deal with as long as the company is individually responsible for the information (RO).

A pharmaceutical industry representative adds that with the exception of the input from readability testing, PILs are written, reviewed, amended and influenced by regulatory/medical professionals and that greater input could be sought from both patients and communication specialists (PI). A HCP also pleas for more patient input as it is generally known that medical information tends to be too comprehensive (HCP). This HCP argues that the text should be tested on a small number of lay people. A communication experts agrees on this and provides the following suggestions in reaction to this:

- Make a difference between "contents" (The EU-Directive states: 'particulars to be mentioned') and "prototype" ('as the reader will see it'). Patients cannot interpret 'contents'. They can interpret what they see when they look at a prototype.
- For a test of PILs, it is essential to establish first what needs to be tested and why. The most critical or risky actions for each medicine should be tested first. Select test participants who are most likely to interpret particular information. Five test participants are enough to find out what is effective and what is not.

It is an iterative process that leads to gradual improvements of visual information. After that, improve through modifying the contents and visual presentation. Test the next version of the prototype again.

- Although all patients can at some point be classified as lay people, it is not appropriate to address them as 'lay-people' if they have a chronic disease. Aiming at lay people only would not provide suitable information for these 'expert patients'. Patients learn about their medicines and gradually and develop from 'lay users' to 'expert patients'. It might therefore be worthwhile to consider - for some medicines - a differentiation in information supply. One example is the use of 'starter-packs' for this purpose.

A regulatory officer (RO) participant brings in a new problem regarding the content, namely that "during the authorisation process regulators and companies mainly concentrate on the scientific assessment. Product information isn't in the focus and often neglected. As a result of scientific discussions there often are last minute adaptions, not considering the patients' needs or any rules, how to provide good patient information".

6.3.6 Risk and benefit information

A result from the stakeholder consultation in Chapter 4 was that much of the advice and information relate to possible side-effects and other warnings. Additionally, it was mentioned that a "section on benefits was missing, to balance the risks presented". We asked participants in the online discussion forum to reflect on this. They came to the conclusion that as for the (long) list of side effects, often consider as off-putting, it is hard to generate consensus regarding which side effects should be included, expect for those requiring immediate action. Again, the issue of "one size does not fit all" comes up here as medicines, situations languages, and EU cultures differ for example. Prescription-only medicines and OTC-medicines are one such example where the risk-benefit decision for OTC products is made in a shop, or while standing in front of a pharmacy-drawer/cupboard at home. The risk-benefit decision for POM is made during a consultation (CE). Moreover, the list of side effects is read by patients at different times for different purposes.

A regulator officer (RO) argues that there definitely needs to be a better balance between the possibility of harm and the likelihood of benefit. Yet, this participant argues that putting the likelihood of benefit in the PIL will go a long way to improving the balance of risk and benefit; using numbers for example is difficult as many people struggle with numbers. In case quantitative statements are added these should be unequivocal, easy to understand and not misleading (PI). A regulatory officer reacts that giving more detailed information than recommended in the QRD-template is a difficult balancing act, as the information may be of promotional nature and encourages inappropriate use of medicine (RO#4). That benefit information should be non-promotional is confirmed by a pharmaceutical industry representative (PI): "The benefit section needs to be balanced against the risks described – patients need and request to know why they are using a particular medicine. The product and its way of action should be described in a non-promotional way".

Participants state that guidance/requirements on this should allow for flexibility depending on medication and therapeutic area as benefits may vary highly across medicines (RO, CE, PI). A pharmaceutical care representative stresses the opportunities electronic media offer by stating that rare and very rare/non-serious side effects might be removed from the PIL if the PIL is supplemented by additional information via electronic media (PI). Another pharmaceutical industry representative

argues however that it is very difficult to determine criteria for leaving out certain side effects (PI): "Patients would perhaps not like having to go to another document to see whether their own adverse experience could possibly be drug-induced, even if very rare. A selection on whether a particular side effect is definitely, probably or possibly related to a medicine is difficult for clinical trials but even more so for post approval pharmacovigilance".

6.3.7 How to communicate important information[26]

Highlighting important information was mentioned as a potential improvement by respondents representing patient organizations . We asked the participants to the online discussion to further reflect on this. They argued that there are different ways to highlight important information (using bold; bigger font, place information up-front at the beginning of the text) (RO/CE/PI). One participant stressed that no matter what method is used to highlight the information, it is important to use the same method consistently (PI#12) while another participant states that standardization in this matter is not the way forward: content and design should go hand-in-hand (CE#8). A regulatory officer is not in favour of highlighting information at all, as patients might tend to read these keywords only and ignore other equally important information. Therefore, it is equally important to ensure that the non-highlighted information is also important and should get patients' attention as well (RO, PI) and that the selection of what is highlighted should be carefully made because if too much information is highlighted, the emphasis will lose its effect (PI). According to this a pharmaceutical industry representative important information that is worth to be highlighted could for example be practical information on what to do if certain side effects are experienced or other precautions that can be taken to prevent harm.

6.3.8 Multilingual PILs

Participants were, at several moments in the online discussion asked about the multilingual PIL and solutions to overcome problems with this type of PIL. One solution might be to combine paper and electronic version by having key information for safe use in the paper version for all languages and the rest of the information available electronically (RO) or to make PILs in all languages available in an electronic format (PI). If PILs are electronically available, it allows patients to choose any language they prefer (PI). Electronic media would also allow to display each language in a user friendly way and people can choose from all languages available (PI). Yet, this might raise problems for migrants, ethnic minorities and the elderly (PI; RO). If web-pages of other languages would be mentioned as being posted on the web-sides, the access to them can again be a problem (HPC). A regulatory officer states that it is important (and legally required), that each pack is accompanied by a paper version that contains all information, legally required and essential for the patient (in all languages). Another solution suggested is to use a booklet format could be assessed for feasibility, with tabs for different languages and/or different colour pages (PI).

6.4 Summary of main results

There is debate among different stakeholders as to which roads to take to improve the PIL. Yet, about some principles there seems to be consensus:

[26] We also asked for the opinion on adding a key information section to the PIL. This issue is addressed in a reported especially devoted on this issues (Van Dijk et al 2013).

- Make best practice examples of aspects of leaflet design (anonymised) available for pharmaceutical companies and include not only the end product but also information on the process of development where possible
- Guidelines on how to compose a good PIL could be improved;
- Including benefit information as well as risk information improves the quality of the information in the PIL;
- Albeit most participants agree that risk information may be shorter, they also have consensus about the fact that it will be hard to decide what information should be kept and what information could be left out.
- To increase patient involvement in the developing process of PILs.

Less consensus can be found for:
- options to reduce the length of the PIL;
- Whether all patients should be able to understand the PIL;
- Whether or not to highlight certain information in the PIL;
- Whether or not to fully use the possibilities of current technologies;
- Whether or not to tailor the PIL more to needs of individual patients.

Chapter 7 Discussion and conclusion

Patient Information Leaflets (PILs) for patients and the Summaries of Product Characteristics (SmPC) for professionals are important pillars of information on medicinal products across Europe. All medicinal products that are authorised by competent authorities of the Member States or by the European Commission are obliged to have both a PIL and a SmPC. While efforts have been made at the EU-level to improve the information provided in the SmPC and PIL (such as the requirement of patient consultation for PILs since October 2005), there is still criticism that these documents are hard to read and understand. This may result in prescription errors causing adverse reactions, or non-adherence to medication because of misinterpretation of the risk for side-effects. The risk of such failures is particularly high among vulnerable patient groups. This report provides an assessment for the European Commission on these two documents.

7.1 Main objective and assessment

The objective of the PIL-S study was to provide the European Commission with an assessment of the readability of the package information leaflets (PIL) and the summaries of product characteristics (SmPC) of prescription and non-prescription medicines. To create this assessment the following steps were taken:

- Identification of possible shortcomings and positive points of the summaries of product characteristics (SmPCs) and package information leaflets (PIL) of medicines as a source of information for healthcare professionals and the public;
- Identification of the causes of such shortcomings and their potential consequences for the health of patients;
- Formulating recommendations in terms of better application of the existing legal framework at EU level in order to improve the SmPC and the PIL in order to increase their value for the healthcare professionals and the general public, as well as their contribution to the rational use of medicines and patient safety.

The assessment was performed using an extensive literature search, a European wide stakeholder survey and online discussion with experts. This summary starts with an overview of the legal context.

7.2 Legal context

Directive 2011/83/EC

Directive 2011/83/EC requires that all medicinal products authorised within the EU are obliged to have a PIL and a SmPC. This holds for products that are authorised authorisation through a centralised procedure as well as for those products that are authorised through a decentralised procedure. The PIL and SmPC have to fulfil the same legal requirements in both procedures. Article 11 of Directive 2011/83/EC describes the information that is required to be included in the SmPC (see page ** of this report). The PIL has to be drawn up in line with the SmPC and its requirements are laid down in article 59 of the same Directive (see page ** of this report). This article mentions eight major subjects to be included in the PIL but also a text that patients should express any suspected reaction to a health professional (or the national reporting system). Another requirement in this article refers to the obligation

to patient consultation to ensure that the leaflet is legible, clear and easy to use. The Directive also pays attention to the comprehensibility of the PIL by stating that the PIL should enable appropriate use (article 62). A first requirement for this is that package leaflets have to be available in the official language or languages if a Member State (article 63). For countries with more than one official language this means that a multilingual leaflet is required.

Guidelines

The European following guidelines are relevant for the Patient Information Leaflet or SmPC:

1. A guideline on Summary of Product Characteristics (September 2009) which explains for each section to be included in the SmPC the information that has to be addressed in that particular section;
2. Guideline on the packaging information of medical products for human use authorised by the community (Final – version 13, February 2008) which has been prepared in order to describe how the provisions of Directive 2011/EC/83 apply in case of an authorisation to granted by the Community (centralised marketing authorisation process);
3. Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, January 2009) which main purpose is "to provide guidance on how to ensure that the information on the labelling and package leaflet is accessible to and can be understood by those who receive it, so that they can use their medicine safely and appropriately" (p.6 of the guideline). Additionally, the guideline includes guidance on how to consult target patient groups for the package leaflet.

QRD templates

The Quality Review of Documents group (QRD) developed templates which provide the official wording that has to be used in the SmPC and PIL in accordance with Directive 2001/83/EC. With the QRDs consistency across different medicinal products and across all Member States is aimed for. The templates define standard headings, standard statements and terms and the format and layout to be used. The QRD-templates provide more practical guidance.

User testing

For all marketing authorisations granted after 30 October 2005, the package leaflet has to be checked and information on patient consultation has to be included in the application dossier. One way to consult patients is through user-testing of the package leaflet. By testing problem areas in leaflet can be identified and improved accordingly.
In the following situations a user consultation is always required:

- First authorisation of a medicinal product with a new active substance,
- Medicinal products which have undergone a change in legal status,
- Medicinal products with a new presentation,
- Medicinal products with particular critical safety issues.

User testing only has to be done in one official language of the EU. Translation has to be undertaken using the process of 'faithful translation'. Yet, such faithful translation has shown to be vulnerable as it can lead to many of the improvements resulting from the testing being lost, as the translators change it back into official-style language(11).

7.3 Patient information leaflet

7.3.1 Problems

There is room for improvement regarding patients' comprehension of the PIL and its readability. The language used is often too complex and the design and lay-out are not always user-friendly. Especially information about interactions, contraindications, dosage instructions and side effects is complex and the use of the verbal descriptors previously recommended by the EC to describe risks (from 'very rare' to 'very common') leads to a clear overestimation of the risks by patients. The elderly and those with low literate skills are disadvantaged, but generally these problems hold for all patient groups. With regard to missing information, our assessment shows that there is a lack of benefit information to be found in the PIL. Small font size, narrow line spacing and the length of the PIL are lay-out related problems most frequently noticed. Consequences of these problems are that readers may give up reading withholding them from important information. This may lead to inappropriate actions such as non-adherence to their medicines. Additionally, patient may get confused or worried for example because of the extensive list of side-effects.

7.3.2 Discussion on solutions

In the literature survey and the stakeholder consultation many ideas to improve the PIL have been brought up. These can be divided into ideas with regard to the PIL itself, as well as with regard to the context in which the PIL is used and also with regard to the development process.

Ideas with regard to the PIL itself

There are many recommendations in the literature to improve the language, structure and design of the PIL. These should preferably simultaneously consider design and content of the PIL as they support each other. Still, here we mention first solutions for individual aspects. We focus on length, font size and line spacing with regard to the lay out and on risk-benefit information with regard to the content. These topics proved to be consistently mentioned in all three types of assessments we performed (literature survey, stakeholder consultation and online discussion). Moreover attention is paid to digital solutions as they were frequently mentioned.

Length

The (visual) length of the PIL is considered a problem as it may stop patients from starting to read it. Recommendations to reduce the length of the PIL include:

- Deleting information that is not relevant to the patient, for example information on all available pack sizes and doses.
- Reducing information, for example making the text on when to contact a doctor shorter by stressing the importance to keep contact with the physician (PI#14).
- The visual length can be reduced by changing the design for example by using landscape instead of portrait paper
- Use of an alternative format such as booklets (which received the highest scores in the stakeholder consultation)

Font size and line spacing

Font sizes are often considered to be too small and are considered important in improving the PIL. From the stakeholder consultation it became clear that patient and consumer representatives preferred a larger font size over a shorter version of the PIL. In the discussion on the PIL, font sizes are still used but their practical relevance is limited because of technical progress in this field. Point sizes differ between different font types. Therefore, it may be better to use the so-called x-height (the vertical dimension of a lower case 'x') instead. This has been suggested in the new German DIN-standard (introduced in April 2013) that states that a minimal x-height must be 1,50 mm. With regard to clear spacing between recommendations from the Canadian 'Clear Print Guidelines' could be used.

Risk-benefit information

Adverse effects are the most discussed topic during this assessment. They need to be included in the PIL but there is no clear consensus both in the literature and among stakeholders as to what adverse effects to include and how to include them. There is only consensus to at least including those adverse effects requiring immediate action. It seems that with regard to adverse effects there is no "one size fits all" as medicines, situations, languages, and EU cultures differ. Flexibility in regulation and extensive user testing are mentioned as solutions to overcome the discussion what adverse effects to include or not. Benefit information is missed in the current PILs while it is important for patients to have such information in order to make a balanced informed decision about their treatment. About the question on how to include benefit information there is no consensus and some fear that including this information may lead to promotional information within the PIL. However, putting the descriptive, textual information about the benefits in the PIL will go a long way to improving the balance of risk and benefit; but using numerical benefit information is generally not supported. A step-wise approach to the development of more benefit information in PILs may be the way forward.

Electronic formats

Electronic formats are frequently mentioned during this assessment for example to further improve the attractiveness for readers with modern habits or with special needs such as blind or visually impaired patients. The paper leaflet is much more bound by technical aspects than new technical solutions. The use of digital sources where all information can be found, while the paper PIL includes the most relevant information while referring to the digital source was mentioned as a solution. However, as long as not all patients have access to digital resources the paper version of the PIL should include all information.

Multilingual PIL

In countries with more than one official language multilingual PILs are obliged. As it needs to contain the same information in all languages it can become large, font sizes become small and line spacing narrow. These problems mentioned for all types of PILs are worse for the multilingual PIL, although the scores for the multilingual PIL were only slightly lower compared to those for other types of PILs included in our analysis. A potential solution is to provide separate PILs for each language, but this may provide problems in fitting into the pill box. Moreover, stakeholders, including patient and consumer organizations, do not favour this option above the current situation. Another solution is to use a booklet format with tabs for different languages and/or

different colour pages. Yet another solution may be the combination of paper and electronic formats. Electronic media would also allow people to choose from all languages available As not all Europeans have access to digital resources yet, this is a solution that can only be introduced in the future. Another problem with regard to multilingual PILs is the fact that the information provided needs to the same for all languages. As stated before, translated PILs have been shown to be vulnerable to going back to more formal language (11).

Ideas with regard to the context in which the PIL is used

The PIL does not stand alone. To reach the goal that patients act appropriately there needs to be a combination of information provided by the health care providers which needs to be supported by the PIL accordingly. Patients receive a lot of information, especially during the first stage of their illness and the PIL is only one part of it. The PIL should be a more integral part of the pharmaceutical treatment instead of being a stand alone. Therefore, it should for example be clear who the source is, as the PIL now refers to many actors and does not 'speak with one voice'.
Therefore, the following considerations with regard to the PIL were formulated in the online discussion:

- relate the contents of a PIL to the contexts/situations in which a medicine is used.
- support and stimulate the dialogue between patients and healthcare providers.
- are reliable and trustworthy to enhance the confidence in the quality of the information.

For all three, it is essential to start from a dialogue with patients about their medicines. The current combination of European legislation, QRD-templates, and guidelines does not include this dialogue to a large extent.

Ideas with regard to the development process and regulation

During the assessments several solutions and recommendation related to the development process and regulation came up. They referred to the improvement of the current guidelines (and QRD template) and the input from patients and improved user testing.

The current guidelines are considered not to be clear in several respects. This holds for example with regard to the recommendations for font sizes and line spacing. The guidelines should include principles of good information design in which content and lay-out are jointly considered. Another issue is that the guidelines are considered to be too restrictive in some respects and that more flexibility is needed as medicines and contexts differ. This also holds for the QRD template that could be less regulated to allow for more flexibility across medicines. Moreover, an expert during this consultation noted that there are conflicts between the obligatory words in the template and the requirement of the amended article 63, paragraph 2 (EU-Directive 2004/27/EC amending 2001/83/EC). The Directive requires that 'Package leaflets must be written and designed to be clear and understandable, enabling the users to act appropriately'. The texts in the QRD template do not always allow this. In order to reach this goal this experts argues that a shift is needed from a 'prescriptive legislation' (you must tell users this, this and this) to a 'performance based legislation' (you must 'enable users to act appropriately')

According to the stakeholders, best practice should be promoted much more. Another recommendation is therefore that EMA and national regulatory agencies could publish PILs as examples of good practice, making it easier for the industry to follow the good

examples. These examples need to be based on tested package leaflets and can vary type face, line space, line length, colour, margins, justification. In the UK, the MHRA has put this in practice. It is recommended not only to show the end result of such good example but also to share the information development process of good examples, for example how the input of patients was organised and included. Since October 2005 it is required that for all marketing authorisations PIL has to be checked and information on patient consultation has to be included in the application dossier. One way to consult patients is by user testing. There have been seen improvements in the PIL after this according to stakeholders. Still, there seems to be room for further improvements for example by using an iterative process of writing - designing - testing that leads to PILs that really 'enable users to act appropriately'.

7.4 SmpC

Compared to the PIL few problems were reported on the SmPC although the literature study showed that the information in the SmPC is not always as complete as it should be and sometimes outdated. The value of the SmPC was discussed in the literature but the stakeholder consultation showed that representatives of HPCs judge the quality of the SmpC as reasonable and find the SmPC valuable in case a professional has questions on issues such as a new medicine, contraindications, interactions with other medicines, therapeutic indications, and dosing. Additionally, most of the current topics addressed in the SmPC are valued as being important and most stakeholders were not aware of problems with the SmPC. However, two recent studies in Germany and the UK showed that SmPCs are not seen as valuable nor often used by physicians.
Information on issues related to children (such as specific dosing) were mentioned as being missing. If problems were mentioned they mainly referred to the fact that the information in some section is too extensive (mentioned by representatives of the pharmaceutical industry) and that there is too much emphasis on regulatory aspects which are not relevant for the HCP (ibid.). In a UK study where SmPCs were user tested (49) it proved that simpler language and more clear structure were helpful for HCPs in finding and understanding information. Also a key information section was valued.

7.5 Limitations of the study

Stakeholders in all EU Member States as well as from other European countries were given the opportunity to reflect on problems and opportunities related to the PIL and SmPC. Despite numerous effort to increase the response, response rates among patient organization representatives and HCP organization representatives was low. Language problems could have played a part in the non-response, at least for patient organizations, as questionnaires were only provided in English. This may be the reason that countries from Central and Eastern Europe were under-represented in the stakeholder consultation. However, given the time limit and the budget of this study it was not possible to provide the questionnaires in all languages of the EU Member States. Another reason may have been that the topic was not considered to belong to the expertise of the own organization - as was expressed by several persons who were approached to participate, especially among health care professionals. Therefore, the results of these stakeholders had to be cautiously interpreted.

7.6 Conclusions and recommendations

Conclusion 1: Room for improvement of PIL more so than for SmPC

Patients' comprehension of the PIL and its readability can be improved. The language used is often too complex and the design and lay-out are not always user-friendly. The elderly and those with low literate skills are disadvantaged, but generally these problems hold for all patient groups. For the SmPC less problems are signalled. Although the information is not always complete and sometimes outdated representatives of HPCs judge the quality of the SmpC as reasonable and value most of the current topics addressed in the SmPC as being important. Still improvements can be made especially with regard to the readability of the SmPC.

Conclusion 2: Adapt guidelines and QRD-template rather than legislation to enhance readability of patient information leaflets

Most of the problems mentioned in the assessment can be handled by improving guidelines. The current guidelines are considered not to be clear in several respects, for example with regard to the recommendations for font sizes and line spacing. Guidelines are also considered too restrictive in some respects. This also holds for the QRD template where information not relevant to the patient could be removed such as information on all available pack sizes and doses, to release valuable space to make improvements in content and layout. A step forward in this regard, taken while this research was taking place, was the removal of the requirement for information on all Marketing Authorisation Holders. The guidelines could include more detail on the principles of good information design in which content and lay-out are jointly considered.

Conclusion 3: Strengthen patient input in developing and testing of PILs

As of October 30, 2005 user testing of PILs is required for new medicines. PILs developed after this requirement has been introduced are considered to be more clear and user friendly, but still improvements can be made. There is a plea for strengthening the input from the patient perspective. This could also help in getting more understanding on how to present risk-benefit information for a particular drug. Additionally, more attention could be paid to the translation of the user-tested PIL into other languages. An important aspects is to keep the "lay-ness" of the user-tested version when the leaflet is translated.

Conclusion 4: Best practice should be promoted

Guidelines and the QRD template provide instructions and help in how to compose a PIL and SmPC. However, they do not provide good examples. Good, user-tested examples (as well as their development process) could be promoted more by EMA and national regulatory agencies, making it easier for the industry to follow the good examples. In the UK, the MHRA has put this into practice. Information technology makes sharing best practice on a large scale possible.

Conclusion 5: Development of a strategy for electronic PIL-formats

Electronic formats bring new opportunities for optimizing patient information leaflets. Currently, not every EU-citizen is prepared for the whole range of opportunities provided by new information technologies. In 2011, 15% of EU citizens had never used the internet, and large variation exists across between Member States. But, as more and more European will gain access it is recommended to the EU to start developing a strategy for the future as to how electronic formats can be used to

provide the information that is now in the PIL in an optimal way to individual EU-citizens.

Conclusion 6: Multilingual PILs can benefit from electronic formats

Multilingual PILs are only user-tested on their content, but not on lay-out and design. Because of their increased content, design and lay-out are important aspects of multilingual PILs. Electronic formats may play an important role in the future especially in multilingual countries, for example by providing a combination of paper and electronic formats where the key information is included in the paper format and the rest can be found in electronic format. Electronic media would also people to choose from all languages available. Until wider access is realised other solutions have to be sought for.

Recommendations to the European Commission

Based upon the above the following recommendations are made:

1. Focus on improvement of the PIL rather than on the SmPC.
2. Consider reformulating the guidelines so that they include more principles of good information design and consider allowing for more flexibility in the information recommended in the QRD template between medicines as long as legislation allows it. Include guidelines on translation that go beyond the principle of faithful translation, in order that the lay language introduced through user testing in the original language is not lost during translation.
3. Further strengthen the input from patients during the development process for example by requiring to:
    - make the user testing process more iterative;
    - user test changes in information required by regulators after the initial user testing
4. Make best practice examples of aspects of leaflet design (anonymised) available for pharmaceutical companies and include not only the end product but also information on the process of development where possible.
5. Examine the potential to use electronic media in the (near) future as an increasing number of EU-citizens gets access to these media.
    a) Explore opportunities these media offer for optimizing the PIL in terms of flexibility of information provided and design.
    b) In doing so, explore and research the opportunities for the PIL to be part of the care process rather than a stand-alone source of information.
    c) Consider how mechanisms to alert patients taking long-term medicines to changes in the PIL could be developed through electronic media.
6. Consider those countries with more than one official language in the electronic media strategy.

References

(1) Bergk V, Haefeli WE, Gasse C, Brenner H, Martin-Facklam M. Information deficits in the summary of product characteristics preclude an optimal management of drug interactions: a comparison with evidence from the literature. Eur J Clin Pharmacol 2005; 61(5-6):327-335.

(2) Wall AJ, Bateman DN, Waring WS. Variability in the quality of overdose advice in Summary of Product Characteristics (SPC) documents: gut decontamination recommendations for CNS drugs. Br J Clin Pharmacol 2009; 67(1):83-87.

(3) Arguello B, Fernandez-Llimos F. Clinical pharmacology information in summaries of product characteristics and package inserts. Clin Pharmacol Ther 2007; 82(5):566-571.

(4) Ursino MG, Poluzzi E, Caramella C, De PF. Excipients in medicinal products used in gastroenterology as a possible cause of side effects. Regul Toxicol Pharmacol 2011; 60(1):93-105.

(5) Medicines and Healthcare products Regulatory Agency (MHRA) Committee on Safety of Medicines Working Group on Patient Information. Always Read the Leaflet. Getting the best information with every medicine. 2005. London, The Stationary Office.

(6) Garner M, Ning Z, Francis J. A framework for the evaluation of patient information leaflets. Health Expect 2012; 15(3):283-294.

(7) Pander MH, Lentz L. Improving the usability of patient information leaflets. Patient Educ Couns 2010; 80(1):113-119.

(8) Dixon-Woods M. Writing wrongs? An analysis of published discourses about the use of patient information leaflets. Soc Sci Med 2001; 52(9):1417-1432.

(9) Pignatti F, Boone H, Moulon I. Overview of the European regulatory approval system. J Ambul Care Manage 2004; 27(2):89-97.

(10) Permanand G, Mossialos E, McKee M. Regulating medicines in Europe: the European Medicines Agency, marketing authorisation, transparency and pharmacovigilance. Clin Med 2006; 6(1):87-90.

(11) Zetshen KK, Askehave I. Lost in translation? When patient information crosses borders. Industrial Pharmacy 32, 11-13. 2011.

(12) Gustafsson J, Kalvemark S, Nilsson G, Nilsson JL. Patient information leaflets--patients' comprehension of information about interactions and contraindications. Pharm World Sci 2005; 27(1):35-40.

(13) Fuchs J, Hippius M, Schaefer M. Analysis of German package inserts. Int J Clin Pharmacol Ther 2006; 44(1):8-13.

(14) Fuchs J, Hippius M. Inappropriate dosage instructions in package inserts. Patient Educ Couns 2007; 67(1-2):157-168.

(15) Mira JJ, Lorenzo S, Perez-Jover V, Navarro I, Martin de Rosales AM, Lara C. Assessment of the quality of medication information for patients in Spain. Expert Opin Drug Saf 2013; 12(1):9-18.

(16) Hamrosi K, Dickinson R, Knapp P, Raynor DK, Krass I, Sowter J et al. It's for your benefit: exploring patients' opinions about the inclusion of textual and numerical benefit information in medicine leaflets. International Journal of Pharmacy Practice 2012;n/a.

(17) Vander Stichele RH, Vandierendonck A, De Vooght G, Reynvoet B, Lammertyn J. Impact of benefit messages in patient package inserts on subjective drug perception. Drug Information Journal 2002; 36(1):201-208.

(18) Shiffman S, Gerlach KK, Sembower MA, Rohay JM. Consumer understanding of prescription drug information: an illustration using an antidepressant medication. Ann Pharmacother 2011; 45(4):452-458.

(19) Nathan JP, Zerilli T, Cicero LA, Rosenberg JM. Patients' use and perception of medication information leaflets. Ann Pharmacother 2007; 41(5):777-782.
(20) Wong IC. Readability of patient information leaflets on antiepileptic drugs in the UK. Seizure 1999; 8(1):35-37.
(21) Raynor DK, Silcock J, Knapp P, Edmondson H. How do patients use medicine information leaflets in the UK. Int J Pharm Pract 15, 209-218. 2007.
Ref Type: Generic
(22) Wolf MS, King J, Wilson EA, Curtis LM, Bailey SC, Duhig J et al. Usability of FDA-approved medication guides. J Gen Intern Med 2012; 27(12):1714-1720.
(23) Zetshen KK, Askehave I. PIL of the month: a study of best practice in EU PILs. J Applied Linguistics and Prof Pract 7.1, 97-120. 2010.
(24) Wolf MS, Davis TC, Shrank WH, Neuberger M, Parker RM. A critical review of FDA-approved Medication Guides. Patient Educ Couns 2006; 62(3):316-322.
(25) Dickinson D, Raynor DK, Duman M. Patient information leaflets for medicines: using consumer testing to determine the most effective design. Patient Educ Couns 2001; 43(2):147-159.
(26) Beime B, Menges K. Does the requirement of readability testing improve package leaflets? Evaluation of the 100 most frequently prescribed drugs in Germany marketed before 2005 and first tikme in 2007 or after. Pharmaceut Reg Affairs 1:120. 2012.
(27) Dickinson R, Hamrosi K, Knapp P, Aslani P, Sowter J, Krass I et al. Suits you? A qualitative study exploring preferences regarding the tailoring of consumer medicines information. Int J Pharm Pract 2013; 21(4):207-215.
(28) Bernardini C, Ambrogi V, Fardella G, Perioli L, Grandolini G. How to improve the readability of the patient package leaflet: a survey on the use of colour, print size and layout. Pharmacol Res 2001; 43(5):437-444.
(29) Clerehan R, Buchbinder R, Moodie J. A linguistic framework for assessing the quality of written patient information: its use in assessing methotrexate information for rheumatoid arthritis. Health Educ Res 2005; 20(3):334-344.
(30) Wallace LS, Roskos SE, Weiss BD. Readability characteristics of consumer medication information for asthma inhalation devices. J Asthma 2006; 43(5):375-378.
(31) Roskos SE, Wallace LS, Weiss BD. Readability of consumer medication information for intranasal corticosteroid inhalers. Am J Health Syst Pharm 2008; 65(1):65-68.
(32) Hirsh D, Clerehan R, Staples M, Osborne RH, Buchbinder R. Patient assessment of medication information leaflets and validation of the Evaluative Linguistic Framework (ELF). Patient Educ Couns 2009; 77(2):248-254.
(33) Fuchs J. The way forward in package insert user tests from a CRO's perspective. Drug Inf J 2010; 44(2):119-129.
(34) Aker J, Beck M, Papay JI, Cantu T, Ellis M, Keravich D et al. Consumers better understand and prefer simplified written drug information: an evaluation of 2 novek formats versus the current CMI. Drug Information Journal 47, 125-132. 2013.
(35) Fuchs J, Hippius M, Schaefer M. A survey of package inserts use by patients. Hospital Pharmacy Europe 2005; 21:29-31.
(36) Pander Maat H, Lentz L. Using sorting data to evaluate text structure: an evidence-based proposal for restructuring patient information leaflets. Technical Communication 2011; 58(3):197-216.
(37) Raynor DK, Dickinson D. Key principles to guide development of consumer medicine information--content analysis of information design texts. Ann Pharmacother 2009; 43(4):700-706.
(38) Dickinson D, Teather J, Gallina S, Newsom-Davis E. Medicine package leaflets - does good design matter? Information Design Journal 18, 225-240. 2010.

(39) Pander MH, Lentz L. Improving the usability of patient information leaflets. Patient Educ Couns 2010; 80(1):113-119.
(40) Bjerrum L, Foged A. Patient information leaflets-helpful guidance or a source of confusion? Pharmacoepidemiol Drug Saf 2003; 12(1):55-59.
(41) Zaghi D, Maibach HI. Survey of safety and efficacy information in drug inserts for topical prescription medications. Am J Clin Dermatol 2007; 8(1):43-46.
(42) Raynor DK, Svarstad B, Knapp P, Aslani P, Rogers MB, Koo M et al. Consumer medication information in the United States, Europe, and Australia: a comparative evaluation. J Am Pharm Assoc (2003) 2007; 47(6):717-724.
(43) Spyker DA, Harvey ED, Harvey BE, Harvey AM, Rumack BH, Peck CC et al. Assessment and reporting of clinical pharmacology information in drug labeling. Clin Pharmacol Ther 2000; 67(3):196-200.
(44) Khurana RN, Lee PP, Challa P. Readability of ocular medication inserts. J Glaucoma 2003; 12(1):50-53.
(45) Bergk V, Haefeli WE, Gasse C, Brenner H, Martin-Facklam M. Information deficits in the summary of product characteristics preclude an optimal management of drug interactions: A comparison with evidence from the literature. Eur J Clin Pharmacol 2005; 61(5-6):327-335.
(46) Arguello B, Fernandez-Llimos F. Clinical pharmacology information in summaries of product characteristics and package inserts. Clin Pharmacol Ther 2007; 82(5):566-571.
(47) San Miguel MT, Martinez JA, Vargas E. Food-drug interactions in the summary of product characteristics of proprietary medicinal products. Eur J Clin Pharmacol 2005; 61(2):77-83.
(48) Savill N, Bushe CJ. A systematic review of the safety information contained within the Summaries of Product Characteristics of medications licensed in the United Kingdom for Attention Deficit Hyperactivity Disorder. how does the safety prescribing advice compare with national guidance? Child Adolesc Psychiatry Ment Health 2012; 6(1):2.
(49) Raynor DK; De Veene P; Bryant D (2013) The effectiveness of Summary of Product Characteristics (SmPC) and recommendations for improvement. Therapeutic Innovation and Regulatory Science, .
(50) Vromans L, Doyle G, Petak-Opel S, Rodiger A, Rottgermann M, Schlussel E et al. Shaping medicinal product information: a before and after study exploring physicians' perspectives on the summary of product characteristics. BMJ Open 2013; 3(8):e003033.
(51) Berry DC, Knapp P, Raynor DK. Provision of information about drug side-effects to patients. Lancet 2002; 359(9309):853-854.
(52) Berry D, Raynor T, Knapp P, Bersellini E. Over the counter medicines and the need for immediate action: a further evaluation of European Commission recommended wordings for communicating risk. Patient Educ Couns 2004; 53(2):129-134.
(53) Knapp P, Raynor DK, Woolf E, Gardner PH, Carrigan N, McMillan B. Communicating the risk of side effects to patients: an evaluation of UK regulatory recommendations. Drug Saf 2009; 32(10):837-849.
(54) Carrigan N, Raynor DK, Knapp P. Adequacy of patient information on adverse effects: an assessment of patient information leaflets in the UK. Drug Saf 2008; 31(4):305-312.
(55) Yin HS, Mendelsohn AL, Fierman A, van Schaick L, Bazan IS, Dreyer BP. Use of a pictographic diagram to decrease parent dosing errors with infant acetaminophen: a health literacy perspective. Acad Pediatr 2011; 11(1):50-57.
(56) Hameen-Anttila K, Kemppainen K, Enlund H, Bush PJ, Marja A. Do pictograms improve children's understanding of medicine leaflet information? Patient Educ Couns 2004; 55(3):371-378.

(57) Katz MG, Kripalani S, Weiss BD. Use of pictorial aids in medication instructions: a review of the literature. Am J Health Syst Pharm 2006; 63(23):2391-2397.
(58) Knapp P, Raynor DK, Jebar AH, Price SJ. Interpretation of medication pictograms by adults in the UK. Ann Pharmacother 2005; 39(7-8):1227-1233.
(59) Webb J, Davis TC, Bernadella P, Clayman ML, Parker RM, Adler D et al. Patient-centered approach for improving prescription drug warning labels. Patient Educ Couns 2008; 72(3):443-449.
(60) Wolf MS, Davis TC, Tilson HH, Bass PF, III, Parker RM. Misunderstanding of prescription drug warning labels among patients with low literacy. Am J Health Syst Pharm 2006; 63(11):1048-1055.
(61) Wolf MS, Davis TC, Bass PF, Curtis LM, Lindquist LA, Webb JA et al. Improving prescription drug warnings to promote patient comprehension. Arch Intern Med 2010; 170(1):50-56.
(62) Davis TC, Wolf MS, Bass PF, III, Middlebrooks M, Kennen E, Baker DW et al. Low literacy impairs comprehension of prescription drug warning labels. J Gen Intern Med 2006; 21(8):847-851.
(63) Davis TC, Federman AD, Bass PF, III, Jackson RH, Middlebrooks M, Parker RM et al. Improving patient understanding of prescription drug label instructions. J Gen Intern Med 2009; 24(1):57-62.
(64) You WB, Grobman W, Davis T, Curtis LM, Bailey SC, Wolf M. Improving pregnancy drug warnings to promote patient comprehension. Am J Obstet Gynecol 2011; 204(4):318-5.
(65) Mayhorn CB, Goldsworthy RC. New and improved: the role of text augmentation and the application of response interpretation standards (coding schemes) in a final iteration of birth defects warnings development. Birth Defects Res A Clin Mol Teratol 2009; 85(10):864-871.
(66) Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K et al. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. Health Technol Assess 2007; 11(5):iii, 1-iii160.
(67) Narhu U. Drug information for consumers and patients - a review of the research. National Agency for Medicines. 2006. Helsinki, National Medicines Agency Finland.
(68) Koo MM, Krass I, Aslani P. Factors influencing consumer use of written drug information. Ann Pharmacother 2003; 37(2):259-267.
(69) Tates K, Zwaanswijk M, Otten R, van DS, Hoogerbrugge PM, Kamps WA et al. Online focus groups as a tool to collect data in hard-to-include populations: examples from paediatric oncology. BMC Med Res Methodol 2009; 9:15.
(70) Krass I, Svarstad BL, Bultman D. Using alternative methodologies for evaluating patient medication leaflets. Patient Educ Couns 2002; 47(1):29-35.
(71) Hughes L, Whittlesea C, Luscombe D. Patients' knowledge and perceptions of the side-effects of OTC medication. J Clin Pharm Ther 2002; 27(4):243-248.
(72) Whatley S, Mamdani M, Upshur RE. A randomised comparison of the effect of three patient information leaflet models on older patients' treatment intentions. Br J Gen Pract 2002; 52(479):483-484.
(73) Raynor DK, Savage I, Knapp P, Henley J. We are the experts: people with asthma talk about their medicine information needs. Patient Educ Couns 2004; 53:167-174.
(74) Schwappach DL, Mulders V, Simic D, Wilm S, Thurmann PA. Is less more? Patients' preferences for drug information leaflets. Pharmacoepidemiol Drug Saf 2011; 20(9):987-995.

Appendix 1.A Main characteristics of relevant studies reporting positive points and potential problems with the PIL or SmPC (Chapter 3)

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
Evaluation of PIL: comprehension and/or readability					
Wong et al., 1999 (20), UK	To audit the readability of PILs prepared for marketed proprietary AEDs in the UK.	Twelve PILs for antiepileptic drugs were compared with six antiepileptic drug articles from medical journals and six headline articles from UK newspapers.	PILs were more readable than the scientific articles and newspapers. The Flesch Reading Ease index and the Gunning Fog test results showed that PILs had a mean readability score of 69 (on a scale of 0=extremely difficult to 100=extremely easy) and a reading age of 8.8 (age should be ≤12 to ensure that most of the population are able to understand), respectively.		The PILs for antiepileptic drugs in the UK are more readable than the newspapers and scientific articles. They are suitable for the reading age of the general adult population in the UK.
Gustafsson et al., 2005 (12), Sweden	To determine how well patients could correctly recognise and comprehend the various information items on PILs, and to explore the reasons underlying poor comprehensibility.	From a list of 165 medicines, which had been prescribed ≥100,000 times in Sweden during 1999, 30 medicines and their accompanying PILs were randomly selected and examined.	When patients are asked to read the PIL they can find and understand the information related to several items.	All leaflets had information concerning 5 of the 10 items listed in the EU Directive. Few leaflets had information regarding car driving, drinking alcohol or what to do if the patients had forgotten to take the medicine. Nine failed to give information regarding potential interactions. Patients (especially older ones) had a low degree of comprehension of information about interactions and contraindications. .	1) Information should be included in the PILs, when missing. 2) Messages should be short and simple.
Fuchs et al., 2006 (13), Germany	A survey was carried out to examine a number of aspects that influence the comprehensiveness and readability of package inserts and the availability of important patient information was examined.	PILs of 68 commonly used drugs in Germany were examined.	All package inserts contained information on therapeutic indication, contraindications, interactions, dosage instruction, possible adverse drug re actions and storage. However, an in-depth analysis revealed some differences.	5 PILs failed to include instructions on measures necessary to deal with contraindications. 36.8% included recommendations on suitable measures for dealing with interactions. 13 PILs provided dosage instructions only in mg of active substance instead of a unit dose. 26.5% included the maximum daily	Patients will probably not fully understand any of the 68 package inserts under study and therefore will not be able to follow the instructions to their best possible benefit. We recommend that every package insert be examined with regard to non-

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
				dose. Advice on the period of use was available in 55 PILs. 39.7% described the time of the day when the medication should be used. 38.5% mentioned the kind of liquid to be used with solid oral medications. 10 PILs missed information on suitable measures when administration errors were made. One PIL gave quantitative information in numbers regarding the frequency of application, nine included the severity of every possible adverse drug reaction. 33.8% gave instructions on correct storage, 41.2% included no instructions on the storage temperature. All 68 inserts included foreign words which are usually more difficult to understand. 98.5% contained non-quantifiable statements. 22.0% contained >2000 words. Only one PIL had a font size larger than 10 pt.	quantifiable statements, foreign words, abbreviations and measures taken to ensure that they contain all the important information using a standardised set of quality criteria.
Fuchs et al., 2007 (14), Germany	The following question was addressed: is it possible to optimise package inserts further, within the existing legal guidelines? Particularly researching options to improve 'locatability' and comprehensibility of information.	Five model PILs and their originals for Enalapril, Repaglinide, Telmisartan, Ibuprofen and Paracetamol were evaluated.		The evaluation of all answers to the 15 questions relating to the package insert contents, showed that the participants had greater difficulty locating the requested information in each original insert (n=5), compared to the corresponding model insert. Additionally, the participants needed a significantly shorter time of 10.9–13.8 min to answer the 15 questions in all model package inserts compared to the corresponding originals time of 14.3–19.6 min. The most frequent problems with locatability and comprehensibility arose in the information related to dosage instruction and possible side	*Recommended to avoid misunderstandings and errors due to inappropriate dosage instruction:* • Every dose should be given in volume or quantity of tablets or capsules respectively. • Use of a table is favourable. • Well-structured information provides clearer understanding. • Non-quantifiable statements should not be used without an additional explanation. • Change of page mid paragraph should be avoided.

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
				effects. The models were rated significantly better in each statement regarding the readability, clarity, comprehensibility and volume of text, however of further importance is the fact that they were found to be more motivating to read.	*Recommended as more appropriate side effect info:* • Insert side effect frequency adjectives explanation in numbers. • Group side effects corresponding to their seriousness. • Use a clear table. • Insert recommendation to contact the doctor or pharmacist if side effects occur.
Nathan et al., 2007 (19), USA	To evaluate whether patients read non–manufacturer-developed leaflets and assess patients' opinions concerning the understandability and usefulness of these PILs.	No specific leaflet: leaflets provided with new and refilled medications.	Majority (70%) of patients read the PIL with respect to new medicines. PIL was found to be easy to understand and very useful,	Some respondents (30%) did not always or often read the PIL. The PIL was considered too long, the print too small, information provided by GPs and/or pharmacists,	Production of concise leaflets.
Shiffman et al., 2011 (18), USA	To determine whether patients understand the materials providing drug information (medication guide (MG), consumer medication information (CMI), and patient package insert PPI) and whether these materials convey the intended information.	Three types of patient information material (MG, CMI and PPI) for an antidepressant medication, blinded to mask the identity of the medication, were evaluated.		Less than 20% of the 52 adults with a high school education or less was able to identify the symptoms of a rare but potentially life-threatening situation that can occur with antidepressant medication and only 62% recalled the risk of teen suicide, which is the sole focus of the mandated medication guide. Respondents with lower literacy scores performed more poorly than those with higher literacy scores.	(Authors' conclusion) Providing patients with materials that have been formally tested for their ability to convey essential information to patients, including low-education and low-literacy patients, is crucial for promoting the safe use of drugs.
Mira et al., 2013 (15), Spain	To assess the readability and comprehensibility of the medication information a patient can find on the Internet or in leaflets in Spain, and to analyze the extent to which Spanish leaflets	131 items of information corresponding to 77 different drugs were rated; 54 leaflets were analyzed.	The EU regulations and the review of the templates for product information seem to be applied in Spain. They seem to have unified the information provided to patients and they get higher quality than other information sources.	The leaflets showed more shortcomings (than info on the internet) with regard to information on the benefits of the medication (17 required substantial improvements, 31.5%), correct forms of storage (13, 24.1%), contraindications (12, 22.2%), side effects (11, 20.4%) and	The information ought to be increased, especially that related to the precautions that the patient must take and indications about possible interactions and complications. Other areas for improvement include

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	and drug information on internet met standard quality criteria from the EU.			precautions to be taken (9, 16.7%).	information on the expected benefits of the drug and on how it should be stored.
Hamrosi K et al 2012 (S1P) UK and Australia	To explore consumers' beliefs and preferences for benefit information in medicine leaflets and examine their understanding and reaction to treatment benefits.	Leaflets based on the medicine clopidogrel, containing textual & numerical benefit information (numerical presented using numbers needed to treat (NNT).	Inclusion of benefit information was positive factor. Many felt textual benefit information offered incentive to take a medicine.	Some had concerns that textual benefit information could create anxiety. The numerical benefit information provoked strong feelings of disbelief and shock. Participants were surprised so few would benefit. Some struggled to understand the NNT and others found it difficult to comprehend. Numerical benefit information appeared to shake participants' faith in drug treatments.	Participants wanted to receive information about the benefits of their medicines. However, they may misinterpret the numerical information provided.
Dickinson R et al 2012 (S2P) UK and Australia	To explore participants' opinions and preferences on tailored written medicines information.	Exemplar leaflet for cardio-vascular medicine based on the ACE inhibitor ramipril -tailored for a man aged 55 with hypertension. Reference to other uses of medicine, children's doses, pregnancy and breast-feeding information were removed.	Participants welcomed concept of tailored information, desiring shorter & more relevant information. Information tailored to their condition or disease was most sought-after, followed by tailoring by age or gender. Most participants welcomed tailored leaflets but overall valued a more personalised approach than the generalised tailored information we provided. Many felt tailoring written medicines information could improve relevance of the information to the individual and potentially encourage them to value it.	Some voiced concerns about the potential for the wrong information being given to patients who would be unable to recognise that it was incorrect. Other concerns included how tailoring might impact upon the quality of information available and the feasibility of delivery (especially legal implications and cost)	A key finding was the participants' desire for a truly individualised approach to tailoring medicines information, as opposed to the generalised tailored information provided in the study. Participants said they would value having spoken communication with a healthcare professional at the same time as they received tailored leaflets.
Raynor DK,	To determine how	Any PIL for a	97% were aware of the leaflet, a	Of repeat users, nearly 60% said	Almost all patients surveyed

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
Silcock J et al 2007 (S5P) UK	patients use patient information leaflets (PILs) for prescription medicines	medicine dispensed in the UK	significant improvement on previous studies. 35% said they had read at least some of the leaflet with this supply. However, this figure was 71% for first-time users, and 87% of repeat users said they had read the leaflet at some time in the past. Side-effects section was most commonly read, and the information in this section was the most common specific reason given for reading the PIL. 11% of first-time users & 15% of repeat users said they had at some time taken action as a result of reading the PIL.	they had never or rarely looked at the leaflet after the first time.	were aware of the PIL, showing that presence of leaflets now being felt. Most read the leaflet with the first supply, although the same cannot be assumed for very old individuals, who were under-represented. A majority taking a medicine long term did not read the leaflet again, after the first time - this is a concern. Much will have been forgotten and some information may have changed. Pharmacists continue to have a role in encouraging the use of PILs.
Wolf MS et al 2012 (S9P) USA Also design	To examine readability, suitability & comprehensibility of medication guides, particularly for those with limited literacy.	Assessments of suitability & readability of 185 medication guides, and sub-study examining change in suitability & readability 2006-2010 among 32 of the medication guides (Study 1); 'open book' comprehension assessment of medication guides (Study 2).		The 185 analysed medication guides had a mean reading level of 10–11th grade. Only one medication guide was deemed suitable in SAM analyses. None provided summaries or reviews, or framed the context first, while very few were rated as having made the purpose evident (8 %), or limited the scope of content (22 %). For Study 2, participants' comprehension of medication guides was poor. In multivariable analysis, low and marginal literacy were independently associated with poorer understanding.	Current medication guides are of little value to patients - too complex & difficult to understand especially for those with limited literacy. Future improvements might begin with evidence-based readability standards and explanation of the purpose of med guides included in the material. Providing a summary that highlights 'need-to-know' content could limit & layer information, so patients can self-tailor the amount of knowledge they want.
Zethsen KK & Askehave I 2010	Analysed a corpus of ten 'PILs of the month' to find out whether they	10 'PILs of the Month' as identified by the MHRA	• Use of second person pronoun – 'you' • Use of imperative: 'Take the	• Specialist or general medical jargon • Synonyms likely to create	Only one leaflet could be said to constitute a real best-practice example; six leaflets

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
(S11P) Denmark Also design	constitute best-practice examples of user-friendliness from a plain language point of view and if so how.		tablets... • Modality; toning down force of the proposals e.g. You may need to stop taking … • Explicit inter-clause relation – e.g. You may have … because …. or You may need to stop X if you … • Use of lay terminology	confusion • Passive form and nominalizations • Complex cause-and-effect relationship • Complex syntax • Long sentences • Illogical structure of information - most important information 'drowned' • Confusing/inconsistent side effect graduation • Too many or vague/imprecise headlines or illogical chronology of headlines. • Cohesion problems – drawing on information which is only provided later. • Direct transfer or remnants from Product Summary. • Information overload - too many and too detailed explanations • Poor layout: too many/too few bullet points, syntactically inconsistent bullet points, too many words in bold print, inconsistent highlighting.	were a mixture of positive and negative features; whereas three leaflets were very far from constituting best practice. A consistent feature of best practice is patient centredness
Vander Stichele RH et al 2002 (S15P) Belgium	To explore the impact of the inclusion of a benefit message in a patient package insert on knowledge about medicines and on subjective benefit/risk perception	PILs for Cisapride and itraconazole	The provision of inserts increased the knowledge about medication in all the intervention groups. 31%,, 41%, and 54% of the subjects who read a normal insert agreed that the benefit of the medicine was greater than its risks, compared to 62%, 64%, and 70% of subjects who read an insert with a benefit message included.		Adding a section on benefit information within a patient package insert helps to integrate increased knowledge about medication into a more balanced benefit/risk perception.
Beime B, Menges K 2012 (S17P) Germany	Based on the "Action Plan 2008/2009 for Improving Drug Therapy Safety" issued by the	100 of the most frequently prescribed medicinal products in Germany were		44% of the 100 most frequently prescribed medicinal products in Germany have PLs with a "normal" or better readability.	Apart from text required to be short as possible, of short sentences, simple and clearly written, other legal

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
Also design	German Federal Ministry of Health, the Federal Institute for Drugs and Medical Devices (BfArM) has launched a study on the effect of readability user tests on the quality of Package Leaflets (PLs).	selected and their readability analysed.		PLs on the market since 2007 show a trend towards improvement when compared with products marketed before 2005. This effect was even more pronounced with the 23 PLs tested as required. The new European legislation in force by the end of 2005 induced a trend towards better usable PLs. On the average, however, this effect is barely recognisable. Only new products on the market need to be tested in regard to readability. Simultaneously, the text extent increased – a considerable effect against the intended improvement.	requirements influence the length of PILs. These conflicts cannot be resolved as long as the entire SmPC needs to be mentioned in the PL due to Medicinal Product Act and liability provisions Nowadays, other (technical) solutions should be legally confirmed to present the content of a PL with a good design in different ways according to the need of each of different user groups.
Evaluation of PIL: design , lay-out and/or structure					
Bernardini et al., 2001 (28), Italy	To evaluate the attitude of patients towards some typographical modifications such as colour, layout and print size in the PIL.	No example PIL used.		Most of the respondents (65.7%) did not like a coloured PIL. A great majority of the respondents said that the print size was too small. Point 10 and 11 sizes were preferred. The great majority of respondents (60.6%) would prefer a more detailed leaflet, and 61.1% said that they would prefer a more schematic and concise leaflet.	Colour: preference for black; Size: use of point 10 or 11; Layout: more detailed but at the same time more schematic and concise PIL.
Krass et al., 2002 (70), USA Also	To develop and compare results using MIDAS and CIRF for evaluating PILs distributed in community pharmacies. The	Thirty-six different PILs were examined: 12 ibuprofen leaflets, 12 amoxicillin leaflets, and 12		Results MIDAS: The majority of leaflets did not meet criteria for line spacing, margins, line length, use of bullet points, bolding/box or summary to highlight important	The potential importance and influence of design quality on the comprehensibility and utility of information leaflets needs to be taken into

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
compre-hensibility	Medication Information Design Assessment Scale (MIDAS) quantifies the extent to which a given leaflet meets various design characteristics. The Consumer Information Rating Form (CIRF) quantifies consumers' perceptions of the comprehensibility, utility and overall design quality of the leaflet.	paroxetine leaflets. Plus three model PILs, one for ibuprofen, one for amoxicillin, and one for paroxetine, corresponding to PILs that were collected from the community pharmacies.		points, upper and lower case letters in headings and text, or true headings separated from text. One third of the leaflets also failed to meet criteria for type size, ink contrast, and font style. Results CIRF: The model PIL received more favourable ratings on utility and comprehensibility. And received significantly higher ratings on six items measuring design quality (organization, attractiveness, print size, spacing, tone and helpfulness). The model PIL was more favourably judged than the pharmacy PIL on the amount of information provided.	account.
Hughes et al., 2002 (71), UK Also compre-hensibility	To assess patients' knowledge about their medicines and the side-effects of their medication. Sources of information were also investigated (PIL included).	PIL provided with OTC medication. Five participants had purchased ibuprofen, four an antihistamine, and one a decongestant.	Reasons for reading a PIL were given as: the medicine was new; a side effect was experienced; the medicine was for a child; it was not a regular medicine.	Only three of 10 participants had read the leaflet. Most common stated reason not to read the leaflet: they have read it on a previous occasion. Problems related to the PIL were: the leaflet design (the writing was too small), information about children's doses was confusing (they would like doses to be related to weight or height, as children of the same age may be very different in size). Main complaint: long list of side-effects would encourage people to wrongly attribute symptoms to their medication, or to "develop" side-effects.	Clearly, information about potential side-effects should be provided to patients, but problems in understanding the leaflets, and "scaring" patients with long lists of side-effects need to be addressed.
Whatley et al., 2002 (72), Canada	To compare the standard textual PIL with two experimental PILs incorporating numerical information or graphical representations of relevant information with regard to the effect on taking the NSAID among	The hypothetical drug was described as a therapy for osteoarthritis or joint pain. Information in the PIL was based on the non-steroidal antiinflammatory drug (NSAID)		Participants who were presented with the standard text-only PIL were less likely to take the medication. The PILs with either numerical or graphical data neither increased nor decreased the likelihood of taking the medication.	Physicians should inquire about patients' perceptions of medication acceptability and encourage open discussion about medication information received from various sources.

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	older patients (>65y).	indomethacin.			
Raynor et al., 2004 (73), UK	To provide an understanding of the experiences of people with a chronic illness with medicines information. *Interesting for PILs project:* To assess patients' views on the current leaflet provision, following implementation of the EU Directive.	PILs included with asthma medication	People want to know what medicines are for, how to use them, how to tell if they are working, and what side effects to watch out for. Individualised information was valued.	Medicine leaflets were generally seen as less helpful than face-to-face advice. Spoken advice is the gold standard. Leaflets were not seen as particularly useful and were often thrown away. The design was disliked, with too much to read, a dull and boring appearance and the type too small. They were folded and creased, making them look unimportant. They felt the information was in the wrong order and that important things did not stand out. They felt that it was standardised information and that not everyone needs all of the information. Information on a leaflet - particularly on side effects - could change without their knowing.	Health professionals need to maximise the impact of the leaflets by emphasising their importance and using them as part of their verbal counselling. Legislators and regulators need to recognise that consumers currently have unmet medicines information needs. People who take medicines should be involved in leaflet development and testing.
Clerehan et al., 2005 (29), Australia	To develop a framework based upon linguistic theory for analysing the text of written patient information and to apply it to methotrexate leaflets currently provided to patients with rheumatoid arthritis.	PIL included with methotrexate.		1) Drug information leaflet has an identifiable generic structure; lack of standard approach. 2) Little agreement between practitioners about the purpose or extent of the information that should be provided. 3) Within the same section, the reader might receive different signals about what to do with the information presented. 4) High lexical density; leaflets appear to be aimed at a more academic scientific reader.	Headings, if in use, need to be transparent and consistent, as they assist patients to find answers to specific questions they have. The text lexical density in PILs need to be near the spoken end, aiming for the 3-4 range.
Fuchs et al., 2005 (35), Germany	To assess expectations and preferences of patients regarding package inserts.	No specific PIL used.	The majority (79.6%) said that they "always" read the package inserts of newly prescribed drugs.	Out of 821 participants, 73.4% said they would prefer "less comprehensive" package inserts, 24.5% agreed with leaving the package insert as it was, and only 2.1% wanted more information According to 76.3% of 822	The structure of the PIL should be (in order of importance): • Name of medicinal product. • Ingredients. • Therapeutic indication and therapeutic group.

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
				participants, a package insert should include "only the most important information"; 8% would have liked additional information; 15.7% were satisfied with the content of the current package inserts. The size of package inserts was criticised by 18.8%. More than 50% of the 197 volunteers who gave comments about package inserts found it difficult to understand the information, and 11.2% felt insecure after reading the inserts.	• Contraindications. • Appropriate precautions for use and special warnings. • Dosage instruction. • Hints for application errors. • Interactions. • Possible adverse drug reactions. • Application form and quantity of the drug. • Storage. • Manufacturer. • Date of the last update of PIL.
Wallace et al., 2006 (30), USA	To assess reading level, text size, dimensions, illustrations, steps and sequences of the consumer medication information (CMI) included with each prescription.	CMI for all prescription asthma inhalation devices available in the US (n=20).		In many cases, the reading level was too high (8.2 +/- 1.5) and text point size too small (9.2 +/- 2.2). Absolute size was inappropriate. Sometimes, instructions were incomplete or in an out-of-order sequence.	Patient education materials should be written at or below 5th to 6th-grade level; the recommendation size for text is 12 pt or larger.
Roskos et al., 2008 (31), USA Also readability	To evaluate 1) readability and font size; 2) length and width; 3) number of illustrations; and 4) directions of use in each of seven consumer medication information (CMI).	Seven CMIs of currently prescribed intranasal corticosteroid inhalers for treatment of allergic rhinitis.	4) Directions followed a logical step-by-step chronological sequence.	1) readability higher than the recommended 5th or 6th grade; font size smaller than the recommended 12 points; 2) dimensions were too small, or too long, or too narrow; 3) illustrations were often times too small with no device-overview diagram,	Increasing paper size would allow for larger, more readable text and accompanying illustrations.
Hirsh et al., 2009 (32), Australia	To obtain patient feedback about the structure and quality of medication information leaflets and to validate the usefulness of the Evaluative Linguistic Framework (ELF) for improving written communication with	Rheumatoid arthritis (RA) medication leaflets.			Patients prefer to have a consistent generic structure to enable easy navigation through the leaflet (they proposed 10 moves in the leaflet), They favoured having the benefits presented before the side effects. The tone needed to be positive, i.e., encouraging or reassuring,

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	patients.				Clear instructions, such as how to take the medication, what to do if side effects occurred, what to do if a dose was missed, should be provided. The grammar needs to be consistent with the purpose of the text. Participants generally liked headings in the form of questions. Vocabulary should not be too technical. Consideration should be given to the lexical density of the text which ideally should be below three or four.
Raynor et al., 2009 (37), UK, Belgium	To 1) identify principles from the large body of evidence associated with the wider discipline of information design; 2) present it in a usable form for people developing written medicines information; 3) assist health professionals in assessing the written information that they are considering giving or recommending to patients.	Content analysis of six texts (from papers, editorials, and books) selected by key informants.	N/A	N/A	Ten ground rules for good document practice: 1) Use short, familiar words and short sentences; 2) Use short headings that stand out from the text; 3) Use a type size as large as will fit in the available space, but retain some white space; 4) Do not fill the page with text; leave plenty of white space; 5) Use bullet points rather than continuous text to organise lists; 6) Use a conversational tone of voice, addressing the reader as you; 7) Use the active or imperative voice: e.g. "Take this medicine"; 8) Use unjustified text (ragged right); 9) Bold, lower-case text is good for emphasis (words in capitals or italics are hard to read); 10) Pictures or graphics do not necessarily improve a document.

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
Fuchs et al., 2010 (33), Germany	To investigate the consequences of the increase in the amount of text in package inserts that has been observed over the last years.	Five original package inserts, available on the German medicine market, and five previously developed model versions were investigated.	There was no general relationship between the comprehensibility and the amount of text; long texts were also well comprehended.	An increase in the number of words in the originals led to a significant decrease in ability to locate the contents. It also meant that the: • First impression of the originals deterred the participants from reading further; • Confidence about using the medicine decreased; • Participants felt worse informed by the information contained in the PILs; • They more frequently did not want similar PILs in the future; • They more frequently expressed the opinion that the PILs contained too much information; • Information provided in the PIL was more frequently difficult to locate; • Information provided was difficult to understand; • They more frequently stated the text was difficult to read.	Shortening PILs is important. Examples: • Avoid repetitions and extensive explanations • Use short points instead of long sentences • Reduce the text that is intended only for doctors. Establishing the right time to carry out user tests and clear rules for harmonization of the PILs should also be considered. Guidelines, templates, and directives should focus more on the relevant aspects and reflect more closely scientific and practical experience. Precise, comprehensible, concise and realistic rules can be better put into practice to achieve shorter, more understandable PILs.
Pander Maat et al. (36), 2011, the Netherlands	To assess the text structure imposed on patient information leaflets in the European Union.	N/A			*Proposed leaflet structure with 4 categories:* 1. 'Medicine – goal and ingredients' includes 'What the medicine is used for', 'Ingredients and medicine group'. 2. 'Usage – directions' includes 'Directions for use' 3. 'Usage – potential problems' includes 'Do not use or take special care', 'Side effects', 'Driving and using machines', 'Pregnancy and breast feeding'. 4. 'Medicine – other aspects' includes 'Packaging and appearance', 'Storage',

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
					'Registration data'.
Schwappach et al., 2011 (74), Germany	To investigate patients' preferences towards content and presentation of drug information leaflets using prepared medication brochures in a discrete choice experiment.	Low dose acetylsalicylic acid served as example drug to generate clinical information.		Participants slightly preferred coloured over black-white leaflets, no visual presentation of quantification of side-effects ("smilies"), provision of a brief summary and general health tips, but no information on what to do in case of side-effects. Older participants had a stronger preference towards less information. Higher educated participants valued inclusion of information about all side-effects and what-to-do information higher compared to individuals with lower educational attainment.	Even among the already restricted age group above 50 years, significant differences between age groups were observed emphasizing the need for age-specific adaptation of the extent of drug information. Our results emphasise the importance of education and proof, that more general information is required especially by higher educated people.
Luk et al 2010 (S3P) Australia	To identify, collate, and evaluate different formats of written medicine information (WMI) from 6 English-speaking countries compared with the US Keystone Consensus Criterion 8 (USKCC8) and the Ten Key Principles (TKP) of Consumer Medicine Information.	157 samples of WMI for 10 prescription and 3 over-the-counter medicines from UK, Ireland, Australia, New Zealand, USA and Canada.	Overall median compliance with USKCC8 was 70%, and 74% to TKP. New Zealand leaflets achieved the highest compliance with USKCC8 (83%) with US leaflets the lowest (55%) Australian and New Zealand leaflets showed the highest compliance with TKP (90%), while UK leaflets demonstrated the lowest (60%)	Overall median reading grades for the leaflets were 10 (Flesch-Kincaid Grade Level) and 11 (Fog).	Performance varied greatly between countries, with readability grades exceeding the recommended range. International examples of WMI show wide variation in compliance with guidelines on recommended format and presentation. These examples of WMI require high literacy to read. Future WMI development should use more recommended formats and increase comprehensibility.
Aker J et al 2013 (S8P) USA	To solicit consumers' preferences about formatting of information, their motivation to read drug information, and their ability to navigate and understand the information.	3 prototypes for 3 prescription drugs, ORTHO TRI-CYCLENTM (norgestimate/ethinyl estradiol), COUMADINTM (warfarin), and PARNATETM (tranylcypromine).	Consumers correctly answered more questions about the medicine when presented with a new (70%-95%) or a bubble prototype (83%-92%) than with the current format (53%-74%). All attributes scored higher with both prototypes compared with the current format.		Key attributes preferred by consumers must be considered as new formats for patient medication information are developed.

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
		The prototypes included 2 novel formats ("new" and "bubble") and "current" format patients now commonly receive with their prescriptions.	In terms of overall preference, consumers favoured the new prototype & indicated they would be more motivated to read it.		
Dickinson D et al 2010 (S10P) UK	• To establish whether good information design makes a difference to the performance of PLs • To attempt to quantify the difference in performance, in ways that make sense to medicine regulators • To link performance differences to specific improvements in design and layout.	2 different presentations of identical text, with and without features of design best practice. Fictitious but realistic-sounding medicine, Atenofen.	• Easily grasped, visible structure • new section headings start in a new column • Hierarchy of headings: point size, type weight, space above and below • Highly legible headings, in larger bold upper/lower case • Well placed line and column breaks • Emphasis carefully managed • Bold text & prominent x-height bullets for especially important text • Visual identifiers used for key messages, such as warning icons, "take action" arrows • Second color to support document structure • Choice of typeface with large x-height for better legibility at small sizes • Text ranged left rather than justified • Narrow column width and moderate column heights • Numbered headings with a contents list to support sequential reading and/or faster location of items		Results suggest that good design makes the difference between a "pass" and a "fail", and assists readers in searching for key information. Pointers for the future: • Landscape with smaller columns • Layouts that reduce text density: wide margins and more white space • Purposeful sectioning: clear and distinct sections helps people find information • Typography reflecting logic: clear typeface, spacing that groups like elements together • Highlighting key messages – with bold text and type size

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
			• Good text/background contrast		
Pander Maat H, Lentz L. 2009 (S12P) The Netherlands	Assess usability of 3 patient information leaflets and attempts to improve them while complying with the current EU regulations.	(1) Oxazepam, a benzodiazepine (2) Bisoprolol, for hypertension, (3) Rosuvastatin, for patients with high cholesterol.	Comprehension of the information, once found, was around 90%. The revisions led to better performance. Information was found faster and more successful. Comprehension scores were higher as well. Evidence based principles: • Integrate information on same topic • Add headings to facilitate text search • Headings which are visually discriminable (using bold, with different font sizes) • Remove bold fonts from body text. • Transform all sentences containing lists into introductory segment followed by a bulleted list. • Move instructions to the beginning of paragraphs and make explicit • Leaflet structure needs to follow readers' pre-existing schemata.	All 3 original leaflets suffered from usability problems, especially problems related to finding relevant information. On average, only 75% of the topics could be located.	Information leaflets must be written, or rewritten, according to Document Design principles. Furthermore, they must be user tested in a rigorous way. Although current EU regulations for patient information leaflets do not guarantee leaflet usability, the leaflets can be improved somewhat within the regulations. However, further research should evaluate the text structure currently imposed on leaflets.
Wolf et al 2006 (S13P) USA Also comprehension	To investigate whether consumer-directed, FDA-approved Medication Guides are likely to be useful to patients with limited literacy.	All 40 Medication Guides available at the time		Average estimated scores showed an 11th-12th grade reading level. None of the 40 met federal recommendations (6th-8th grade level). Most Medication Guides were deemed unsuitable because they did not provide a summary of content (90.0%) or limit the scope of information (77.5%).	Medication Guides in their current form are not likely to be useful to patients with limited literacy skills. Reading level of text in Medication Guides should be reduced, summaries or "highlights" provided, and the scope of information limited to increase the likelihood of use

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
				Only 23.0% of patients reported having looked at Medication Guides or other accompanying patient information materials; patients with low literacy were less likely to have looked at them (16.7% versus 32.9%, p = 0.03).	among individuals with limited literacy. Consumers should be involved in their development.
Dickinson D et al 2001 (S16P) UK	To compare consumers' ability to use a leaflet based on the EC model leaflet and an alternative leaflet based on best practice in information design).		• Extensive use of bullet points • Use of broken paragraphs • Jargon removed	The target that each question should be answered correctly by 16 out of 20 consumers, was achieved for three of the 15 points in the EC leaflet, compared with eight in the Mark II leaflet. Open questioning confirmed the problems with the EC leaflet, including a failure to understand key concepts about medicine interactions and contraindications	This research demonstrates the benefits of consumer testing, ensuring that leaflets are patient-orientated. A rigid model leaflet would prevent these benefits from being utilised.
Evaluation of PIL: completeness and/or consistency of information					
Bjerrum et al., 2003 (40), Denmark	To examine if PILs on different brands of generically identical drugs contain inconsistent and diverging information that may lead to confusion.	PILs included in different packages of captopril tablets.		Inconsistent information was found with regard to reasons for taking the drug, adverse effects, drug-drug interactions and precautions and considerations concerning pregnancy and breastfeeding.	Initiatives should be taken to coordinate information in PILs covering the same generic product.
Zaghi et al, 2007 (41), USA	To ascertain whether inserts in US-sold topical prescription drugs are deficient with respect to key safety and efficacy information required by the US FDA.	15 inserts of topical prescription medications sold in the US are assessed.		One (7% of the sample) insert (fluorouracil) contained information regarding the drug's effect on pregnancy in humans. This drug caused severe teratogenic effects when used in pregnant women. Two (13%) drug inserts (hydrocortisone probutate, ketoconazole) contained information regarding use in nursing women. Five (33%) inserts (hydrocortisone probutate, clotrimazole, betamethasone dipropionate, mupirocin, permethrin,	To improve drug inserts these deficiencies must be addressed. A safety index for nursing, pediatric, and geriatric patients detailing how dangerous the drug can be to these populations needs to be implemented. *Ways to improve drug inserts:* • Provide a vehicle for diagnostic patch and photopatch testing • Provide contact information

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
				nystatin) contained information regarding pediatric use. One insert (7%) (calcipotriene) contained information regarding use of the drug in geriatric patients. Four inserts (ketoconazole, benzoyl peroxide, clindamycin sulfacetamide, nystatin) described what a patient should do if an administrative error was made.	for a dermatologist or other medical source on staff • Provide information on topical drug interactions with any skin-care products • Stability after tube or jar opening • State the ideal dose in µg/cm2 as determined from efficacy studies • Provide a safety index for nursing, pediatric, or geriatric patients
Raynor DK, Svarstad et al 2007 (S4P) UK, USA, Australia	To evaluate the quality of patient information leaflets provided with dispensed medications in the United States, United Kingdom, and Australia.	Patient information leaflets for atenolol, glyburide (glibenclamide), atorvastatin, and nitroglycerin (glyceryl trinitrate) from the United States, United Kingdom, and Australia.	Leaflets from Australia received a mean overall score of 90% adherence with criteria, those from the UK 81% and those from US 68%.	US leaflets achieved 50% or less adherence for contraindication and precaution information. Omissions included warnings about pre-existing allergy and illness and information about drug interactions. US leaflets also scored poorly (60%) for legibility and comprehensibility. Lower UK score reflected shortcomings in information about how to use and monitor medications (46% adherence) & on adverse drug reactions (64%) - largely due to lack of clear advice about urgency of action related to side effects.	Leaflet quality varied more among the three countries than within each country, reflecting the regulatory context. Australian leaflets performed well across all criteria, whereas US leaflets had significant shortcomings with the omission of vital information for the safe and effective use of the medications. A repeat survey is needed to assess whether new legislation and guidance in all three countries successfully addresses the shortcomings identified.
Evaluation of SmPC					
Spyker et al., 2000 (43), USA	To develop and pilot a method (using a systemised scoring approach) to assess the quality and completeness of clinical pharmacology information in a representative sample of package inserts (=SmPC)	A random sample of package inserts (n=76) was assessed.		Five core information categories were rated on completeness: 1) mechanism of action; 2) pharmacodynamics; 3) drug metabolism; 4) pharmaco-kinetics; 5) dose adjustment. The median for the total Core Information was 31% (range: 4-98%) suggesting that in general,	A periodic assessment of drug labeling by an independent professional society is recommended. They could further develop appropriate methods for this routine assessment and publish the results in the print media and electronic media. They could also increase the motivation

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
				current package inserts lack basic clinical pharmacology information.	of manufacturers to improve the quality of drug labeling through a system of recognition and awards for manufacturers that demonstrate improvement in the labeling.
Bergk et al., 2005 (45), Germany	To compare comprehensiveness and accuracy of drug interaction information in the German SPC with current evidence from the literature and to evaluate the SPC's usefulness with respect to management of drug interactions.	Clinically relevant pairs of compounds with drug interaction (in total 579 pairs).		Overall, for 192 of 579 (33%) evaluated drug pairs, the quality of information in the SPC was equal to the evidence from the standard sources with respect to all five evaluation criteria. Of the 91 drug interactions missing in the SPC, 43% were mentioned in all three standard sources. Only in 61% of the pairs listed in the SPC was the interacting drug mentioned as a specific compound. For 30 interacting pairs, the precise effect was either not described at all or the effect of the drug interaction as described by the SPC differed from the published evidence or was not specified in sufficient detail to allow for appropriate management. For the majority of the pairs with insufficient management recommendations, recommendations were completely missing. Recommendations for dose adjustment were evaluated in 251 combinations.	To meet the SPCs claim of being the basis of information for health professionals on how to use medicinal products safely and effectively, information on drug interactions should be thoroughly up-dated and expanded.
Vromans et al 2013 Germany BMJ Open 2013;3:e003033 doi:10.1136/bmjopen-	To establish, in the context of the revised European Pharmacovigilance Directive and based on physicians' perspectives, how Summaries of Product Characteristics (SmPCs) could be more	SmPCs in general and then SmPC for simvastatin specifically	Physicians confirmed the importance of SmPCs as a comprehensive source of medicinal product information	Physicians , were moderately satisfied with the current SmPCs, utilised it infrequently and were more likely to engage additional sources of information.	A newly created SmPC version was consistently preferred over the current version. It differed in the way information for particular patient groups was presented, included additional sections (synopsis, checklist for patient information) and used a

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
2013-003033	user friendly and better support physicians' interactions with patients, thereby improving patients' own understanding of their medicines.				tabular format. Physicians indicated that SmPCs should be available with search and hyperlink functions, as well as be automatically updated and integrated in available practice software or similar solutions.
Raynor et al 2013 UK Therapeutic Innovation and Regulatory Science DOI: 10.1177/2168479013501311	The objective was to understand the effectiveness of the SmPC document in communicating essential information to prescribers.	SmPCs for a generalist medicine (Lariam; an anti-malarial) and specialist medicine (CellCept; an immune-supressant)		In their current format, SmPCs are of low perceived value to prescribers, and not central to the clinicians' prescribing behaviour. Current content and presentation of SmPCs, whilst meeting regulatory approval standards, contributes little to the safe and effective use of medication in practice. Of the 15 points of information tested, for the original Lariam SmPC, 6 met the target of 90% to find, and 90% of those to understand, whereas for the final version of the CellCept SmPC, 11 points of information met this target.	1. Revise and simplify heading structure, particularly replacing 'Clinical particulars' with 'Dose and how to use'. 2. Increase the visibility of the headings and sub-headings. 3. Add a key information section to the start of the document. 4. Add a listing of main headings, after the key information section. 5. Use simple language and shorter sentences. 6. Use bullet points to improve readability, particularly for listings. 7. Use a direct style of writing – active not passive. 8. Place related information together in one place. 9. Place information where readers would expect to find it. 10. Make SmPCs available both in hard copy and web-based versions
Arguello et al., 2007 (46), Spain	To assess clinical pharmacology information found in SPCs of European drugs and to compare it with information in their	Completeness of information in 108 PILs and 91 SPCs.	All PILs and SPCs scored as ''complete'' for the item ''identification of active substances''. The most frequently answered items in the PILs were ''identification of active	The average score of PILs for core information was 15.9% (7.94 points out of 50 points). The average score of the SPCs was 35.2% (17.62 points out of 50 points). Three of the 31 analysed items regarding clinical	As an official source of information for healthcare professionals, the clinical pharmacology information provided in SPCs must be made more comprehensive

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	package inserts.		substances'', ''implications of no-compliance and intermittent dosing'', and ''identification of the principal physiological effects''. For SPCs, these items were ''identification of active substances'', ''description of the mechanism of action'', and ''identification of the principal physiological effects''.	pharmacology information did not appear in any of the SPCs studied. Thirteen items did not appear in the PILs.	and should be more accessible.
Savill N, Bushe CJ 2012 (S1S) UK	Aim: to assess any disparity and potential areas of confusion for prescribers through a review of Contraindications sections of the SPCs of all medications currently licensed for treatment of ADHD in the UK - compared with UK national guidance with	SPCs of all medications currently licensed for treatment of ADHD in the UK (7 medications)		Significant differences exist between SPCs & national guidance part due to ongoing reactive process of amending the former as new information becomes known. In addition, recommendations are made outside UK SPC licensed indications and a significant contraindication for methylphenidate (suicidal behaviours) is missing from both NICE & SIGN guidelines. Particular disparity exists relating to monitoring for suicidal and psychiatric side effects.	Clinicians seeking prescribing advice from critical independent sources of data, such as SPCs and national guidelines, may be confused by the disparity that exists. There are major differences between guidelines and SPCs and neither should be referred to in isolation. The SPC represents the most relevant source of safety data to aid prescribing of medications for ADHD as they present the most current safety data in line with increased exposure. National guidelines may need more regular updates.
Wall AJB et al 2009 (S2S) UK	Section 4.9 of SPC was examined for advice on gut decontamination. Data were compared with standard reference sources for clinical management advice in poisoning. Graded • 'A' if no important differences existed, • 'B' if differences were noted but not thought	SPCs for all drugs in the central nervous system (CNS) category of the British National Formulary.		SPC documents were examined for 258 medications from 67 manufacturers. The overall agreement was 'A' in 23 (8.9%), 'B' in 28 (10.9%) and 'C' in 207 (80.2%). Discrepancies were due to inappropriate recommendation of induced emesis in 21.7%, gastric lavage in 38.4%, other gut decontamination in 5.8% and failure to recommend oral activated	Gut decontamination advice in SPC documents with respect to CNS drugs was inadequate. Possible reasons for the observed discrepancies and ways of improving the consistency of advice are proposed.

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	clinically important, • 'C' if differences were thought to be clinically significant.			charcoal in 57.4%.	
San Miguel MT et al 2005(S3S) Spain	The aim was to assess the information about food-drug interactions with potential clinical relevance as it is described in the SmPCs of the authorised medicinal products in a European Union country (Spain).	The SmPCs of the medicinal products containing selected active substances were examined with emphasis on food-drug interactions.		Frequently, information on food-drug interactions in SmPC in Spain does not fulfil current recommendations, both in quantity and quality. Available data reveal food-drug information only mentioned in 72.7% of all SmPC where it should be and only found in specific section for interactions in 36.0% of all cases. Description & agreement with recommendations for each SmPC item ranged between 4.2% and 36.0% and between 31.8% and 49.0%, respectively.	The SmPC is a suboptimal source of information for food-drug interactions.
Evaluation of the presentation of risk information in consumer medication information (not specifically PIL)					
Berry et al., 2002 (51), UK	Four studies of more than 750 people, whom were asked to estimate the probability of having a side-effect on the basis of qualitative (from 'very common' to 'very rare') and quantitative descriptions (from >10% to <0.01%) were conducted.	N/A		Pilot study (200 undergraduate students): gross overestimation of the risk of side-effects from qualitative descriptors. Second study (112 adults): estimated mean probability of having the side-effect was 64% if given the qualitative description; 20% if given the numerical value. Third study (360 adults): those given the term 'common' rated risk as 50%; those given the equivalent numerical value of 2% rated risk as 9·5%. Those given the description rare rated risk as 21%; those given 0.02% rated risk with 7%.	The results strongly suggest that the qualitative descriptions recommended by the EU lead to gross overestimation of risk, with results from all four studies showing a similar level of overestimation.
Berry et al., 2004 (52), UK	To investigate people's interpretation of risk in relation to OTC	Ibuprofen		Those who received the verbal descriptor were significantly less satisfied with the information	We would recommend that the EC stops advocating the use of particular verbal

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	medicines *Compared statements: "This effect occurs in 6% of people who take these tablets" (numerical) versus "This effect is common in people who take these tablets" (the corresponding EC verbal descriptor).* And to examine how people interpret EC recommended 'action' labels if a side effect occurs (unexplained wheezing or shortness of breath). *Compared statements: If you experience this side effect you should seek medical help 'immediately' versus 'as soon as possible'.*			provided, and rated the side effect severity and likelihood of occurrence to be significantly higher than those who received the numerical descriptor. They also perceived risk to health to be significantly greater and rated intention to take the medicine to be significantly lower. There was also a highly significant effect of presentation mode on participants' probability estimates, with those in the verbal condition producing a mean estimate of 56.6% compared with 19.9% for those in the numerical condition. There was no reliable difference between people's interpretation of the terms 'immediately' and 'as soon as possible'.	descriptors to describe risk, or recommended actions, until there is clear empirical support for their use. We also suggest that the effectiveness of alternative methods of information presentation, such as pictograms or graphical displays, be investigated. Such presentation formats might not only lead to more accurate interpretations of probability, but may be more suitable than the verbal and numerical formats, for a broad sector of the population (including those with lower levels of literacy).
Carrigan et al., 2008 (54), UK	To examine the method used to describe the likelihood of adverse effects, and the format of this information in the information leaflet. And to determine whether it met the requirements of the EU guidance.	PILs supplied with 50 most frequently prescribed drugs in England. 25 branded products and 25 generic drugs.		Twenty of 50 leaflets (40%) gave no indication of the likelihood of adverse effects occurring. Six (12%) used the recommended EU terms and a further 20 (40%) used a wide range of other verbal descriptors. Only four leaflets (8%) provided any form of numerical indication of risk. Over half (52%) presented long lists of adverse effects in paragraphs of continuous text.	Patient need is not being met in terms of the provision of usable information about the likelihood of adverse effects.
Knapp et al., 2009 (53), UK	To investigate the effectiveness of presenting medicine side effect risk information in three different forms: 1) verbal descriptors, e.g. 'common'; 2) absolute	Risk of side effects occurring when (hypothetically) using tamoxifen.	Those in the absolute frequency format demonstrated greater accuracy in estimating the likelihood of having two of four side effects than the other two formats. They were also more accurate at estimating the		People overestimate the risk of side effects, irrespective of the manner in which information is presented. Nevertheless, participants who received side effect information in the frequency

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	frequencies, e.g. 'less than 1 in 10 people'; 3) a combination of verbal descriptors and frequency bands, e.g. 'common (affects less than 1 in 10 people)'.		likelihood of themselves or the average person having any side effect of taking tamoxifen. Participants in the absolute frequency format rated the risk to health from tamoxifen as lower than those in the other two formats, were more satisfied with the information they received than those in the verbal format, and felt there would be less impact of the information on tamoxifen use than those in the combined format.		format were significantly more accurate at estimating the risk of side effects than the other two formats (verbal and combined). People are less accurate at estimating side effects that are less frequent. The findings highlight the deficiencies in using verbal descriptors for conveying side effect risk, and the strength of using absolute frequency descriptors,
Evaluation of the use of pictograms in medication information (not specifically PIL)					
Hameen-Anttila et al., 2004 (56), Finland	To test whether children understand the *USP pictograms* (n=15) and if these pictograms improve understanding of PILs (one half of the participants read the leaflet about penicillin-V only, the other half read the same PIL with pictograms and were asked seven questions to assess understanding).	PIL for oral penicillin-V.	Group of children with only PIL did not have a different understanding of the information provided in the PIL from the group of children who saw the PIL with the pictogram.		When pictograms are placed in the context of leaflets, their usefulness is not so evident.
Katz et al., 2006 (57)	Literature review on the shortcomings of traditional consumer drug information, synthetise published evidence evaluating the use of pictorial aids in patient education materials, and highlight the use of such aids in high-risk populations, including patients with limited literacy skills.	N/A		1) small print size (normally requires an visual acuity of at least 20/50, making it hard to read especially for elderly. 2) written at a reading level that is too advanced for most consumers.	Mismatch between reading skills and consumer drug information exposes the inherent difficulties that low-literacy patients face when trying to interpret medication information. Pictograms enhanced comprehension and adherence of patients when PIL with and without pictograms were compared. Pictograms need to be used in combination with written and

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
					oral instructions.
Yin et al., 2011 (55), USA	To investigate whether a *pictographic dosing diagram* could improve parent ability to dose infant acetaminophen, and to determine whether pictogram benefit varies by health literacy level. *Comparison of text-only and text + pictogram instructions.*	200 products representing 99% of the U.S. market share of pediatric OTC analgesic, cough/cold, allergy, and gastrointestinal liquid products.	Text + pictogram recipients were less likely to make an error compared to text only recipients, Of text +pictogram recipients, 0.6% made a large overdosing error compared to 5.6% of text-only recipients. Pictogram benefit varied by health literacy, with a significant difference in dosing error evident in the text + pictogram group compared to the text-only group among parents with low health literacy, but not for parents with adequate health literacy.		Inclusion of pictographic dosing diagrams as part of written medication instructions for infant acetaminophen may help parents provide doses of medication more accurately, especially those with low health literacy.
Knapp et al 2005 (S6P) UK	To compare 2 sets of pictograms for instructions or warnings (from US & South Africa) for understandability by adults in UK & examine the effects of pictogram size and repeat presentation on understandability among older adults.	No PIL involved – eligible?? - but findings are relevant	Pictograms for 10 different instructions and warnings showed great variation in interpretation rates (7.5–90%), with few significant differences between US & South African versions.	Only 3 were understood by ≥85% of the population. Pictograms performed significantly better if they were larger and at the second presentation	This study shows that some existing pictograms are not easily interpreted and that testing is needed before their implementation. A reduction in size to allow incorporation into conventional written formats may cause additional problems for patients.
Evaluation of prescription drug warning labels					
Davis et al., 2006 (62), USA	To identify factors associated with patient understanding of prescription warning labels (PWLs).	Eight commonly used PWLs were assessed.	Simple, routine tasks using uncomplicated words, such as take with food, were understood by patients.	High lexile scores (difficult to read). Information written on 1st-grade level might not be clear to patients. PWLs are not likely to be useful to patients in their current form, especially to those with low literacy skills. This could result in misuse of medication.	Health information in printing labels should have a lexile score below 6th grade. Use, at all times, of familiar working and concepts.
Wolf et al., 2006 (60), USA	To explore the causes for misunderstanding text and icons on eight prescription drug	Eight PWLs: 1) Take with food; 2) For external use only; 3) Medication		With the exception of the label "Take with food," less than half of all patients were able to provide adequate interpretations of the	The PWLs were not helpful to patients with low literacy skills. Causes for misunderstanding were

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	warning labels (PWLs) among patients reading at or below the sixth-grade level (low literacy).	should be taken with plenty of water; 4) Do not chew or crush, swallow whole; 5) Refrigerate, shake well, discard after (date); 6) Do not drink alcoholic beverages when taking this medication; 7) Do not take dairy products, antacids, or iron preparations within one hour of this medication; 8) You should avoid prolonged or excessive exposure to direct and/or artificial sunlight while taking this medication.		warning labels' messages. Respondents frequently became confused when interpreting the multiple-step instructions or did not address all messages of the PWL in their response. Many of the icons used on the PWLs appeared to confuse patients. This was especially true if the text was difficult to comprehend. Thirty-one patients (41.9%) applied cognitive valuation of colour (red, yellow, green/white/blue) to the PWLs. Text messages on certain PWLs, regardless of Lexile score, were not understood by most patients.	attributed to one or a combination of problems associated with label text (word choice, message length, and number of steps for action), icons, and colour. *Opportunities for improvement:* 1) develop standards, regulations, guidelines, 2) involve consumers, 3) seek universal acceptance and consistent use of label icons, 4) train professionals in literacy issues and communication, 5) simplify text, 6) minimise the action sought per label, 7) give meaning to colour and standardise its use, 8) aim for message concordance across languages.
Webb et al., 2008 (59), USA	To refine and pilot test 'consumer-improved' prescription drug warning labels that are easily understood by a diverse set of individuals, including those with limited literacy.	Comprehension of the 10 most commonly used drug warning labels was determined.	Accompanying text on 10 of the most common and important drug warning labels currently in use among a large proportion of pharmacy practices in the US. *Note: Table 2 in the article includes the existing and revised drug warning text and icons*	Most text messages were confusing and used language that was too difficult to understand. Participants preferred using simple language in the most concise manner as well as more practical descriptions. Many also commented that certain language in the existing messages was implicit and unnecessary. The icon associated with ''For external use only,'' was most disliked by participants, as it was confusing and discordant with the text message it was trying to support. When asked about the necessity of icons, most participants favoured having them included in the warning messages, as	The involved participants preferred more parsimonious, direct, and actionable instructions. The resulting warning labels demonstrate more comprehensible icons and simplified text that were in concordance with one another and with patient feedback.

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
				they helped when comprehending the message. The word ''Important'' was determined as the best heading to be placed on the bottle to draw attention to the warning labels (instead of "Warning", "Caution" or "Danger").	
Davis et al., 2009 (63), USA	To test whether the use of more explicit language to describe dose and frequency of use for prescribed drugs could improve comprehension, especially among patients with limited literacy.	Instruction labels for three commonly prescribed medications: glyburide, metformin, and atenolol.		Patients were significantly more likely to understand instructions with explicit times periods (i.e.,morning) or precise times of day compared to instructions stating times per day (i.e., twice) or hourly intervals (89%, 77%, 61%, and 53%, respectively). The prevalence of incorrectly interpreting one or more label instructions among patients with adequate, marginal and low literacy was 71%, 84%, and 93%, respectively.	More explicit language instructing patients when to take the medicine using time periods were better understood compared to instructions that more vaguely stated the number of times per day or hourly intervals.
Mayhorn et al., 2009 (65), USA	To determine whether teratogen symbol warning components could be improved further, whether adding text enhanced comprehension uniformly across symbols, and whether results varied by the application of different interpretation standards (coding schemes).	11 warning labels were examined: 4 new symbols plus the existing baseline symbol, each in versions with and without text, plus a text-only condition.			Specifically, coding schemes for interpretation correctness interact with modifications to the warnings (i.e., the inclusion of text) and with participant characteristics. Text affects symbols differentially. Selection of a symbol should consider symbol performance both with and without text together, not simply one or the other. Several symbols, in both symbol 1 text and symbol-only formats, performed better than the existing symbol.
Wolf et al., 2010 (61), USA	To evaluate whether the use of enhanced drug warning labels improve patient comprehension	Nine warnings were assessed. Each warning had three versions (standard,		Overall rates of correct interpretation of drug warnings varied among standard, simplified text, and simplified text+icon labels (80.3%,	Auxiliary warning labels that had explicit, easy-to-read messages significantly improved rates of attendance

Author, year, country	Objective of study	Involved (type of) medication	Positive points of PIL or SmPC	Problems with PIL or SmPC	Recommendations for improvement of PIL or SmPC
	beyond a current practice standard.	simplified text, and simplified text+icon) for a combined total of 27 labels under evaluation.		90.6%, and 92.1%, respectively). Simplified text labels (with or without icons) were more likely to be attended to by patients than standard labels. Simplified text+icon labels were better attended than simplified text only or standard labels. Among the 3328 patient attempts to interpret drug warnings, 403 (12.1%) were coded as incorrect. Both label type and label order was associated with attendance to drug warning labels. Older age, male sex, and fewer years of schooling were independent predictors of poorer attendance to drug warnings. An interaction was found between label type and literacy level. PWLs with simplified text and simplified text+icons were also more likely to be correctly interpreted compared with standard labels. Low literacy level was an independent predictor of misinterpretation. Patients with marginal and low literacy skills were better able to correctly interpret warning labels with simplified text+icons compared with labels with simplified text only.	and comprehension among patients. The inclusion of icons on warning labels, developed with patient feedback, was found to further improve attendance and correct interpretation among individuals with low literacy skills.
You et al., 2011 (64), USA	To evaluate the effectiveness of a labeling strategy intended to improve comprehension of a teratogen warning.	Comparison of label types: current standard vs. simplified text vs. simplified text + icon.			Comprehension of the icon label was significantly higher than for the standard and simplified text-only labels.

Appendix 1B List of excluded studies based on full text assessment

To recall the selection criteria (as presented in paragraph 3.1.1.) a study must meet to be included in the literature study:

(1) The publication has as (one of) its main subject(s) the package information leaflet and/or the summary of product characteristics;
(2) The publication refers to potential problems with the PIL or SmPC such as finding and/or comprehending relevant information from PILs or SmPCs by patients and/or users, implications for patient safety, unclear lay-out or design, etc.;
(3) The publication addresses the PIL or SmPC within the geographical context of at least one EU Member State or candidate MS, or EFTA-members; in case the publication refers to health literacy or comprehension issues regarding information on medicinal products, publications from other Western (Anglo-Saxon) countries will also be included;
(4) No limit will be set on language of the summary, to enable assessment of possible fall out of summaries in languages other than English, Dutch, German, French, Portuguese or Spanish;
(5) The publication is a professionally or scholarly 'sound' publication, i.e. a scientifically peer reviewed study or a publication from a governmental or professional association.

Table 3A1: List of excluded studies after reading full text with reasons for exclusion, ranked by publication year.

Database	Year	Authors	Title	Reason exclusion
PubMed	2011	Buckley NA, Rossi S.	Bringing greater transparency to "black box" warnings.	Criteria 2, 5 not met
PubMed	2011	Duke J, Friedlin J, Ryan P.	A quantitative analysis of adverse events and "overwarning" in drug labeling.	Criteria 2, 5 not met
PubMed	2011	Costa-Paiva L, Gomes DC, Morais SS, Pedro AO, Pinto-Neto AM.	Knowledge about osteoporosis in postmenopausal women undergoing antiresorptive treatment.	Criteria 1, 2 not met
PubMed	2011	Panagiotou OA, Contopoulos-Ioannidis DG, Papanikolaou PN, Ntzani EE, Ioannidis JP.	Different black box warning labeling for same-class drugs.	Criteria 2 not met
PubMed	2010	Devraj R, Butler LM, Gupchup GV, Poirier TI.	Active-learning strategies to develop health literacy knowledge and skills.	Criteria 1, 2 not met
PubMed	2010	Winterstein AG, Linden S, Lee AE, Fernandez EM, Kimberlin CL.	Evaluation of consumer medication information dispensed in retail pharmacies.	Criteria 1, 2 not met
PubMed	2010	van Hunsel F, van der WC, Passier A,	Motives for reporting adverse drug reactions by patient-	Criteria 1, 2 not met

		van Puijenbroek E, van Grootheest K.	reporters in the Netherlands.	
PubMed	2010	Wallace LS, Keenum AJ, DeVoe JE.	Evaluation of consumer medical information and oral liquid measuring devices accompanying pediatric prescriptions.	Criteria 1, 2 not met
PubMed	2010	Miller MJ, Allison JJ, Schmitt MR, Ray MN, Funkhouser EM, Cobaugh DJ et al.	. Using single-item health literacy screening questions to identify patients who read written nonsteroidal anti-inflammatory medicine information provided at pharmacies.	Criteria 2 not met
PubMed	2009	Conde Garcia MC, Fernandez Feijoo MA, Calleja Hernandez MA.	[Study of rituximab efficacy, cost, safety, and compliance of its package leaflet in a tertiary hospital].	Criteria 2 not met
PubMed	2008	Velo G, Moretti U.	Direct-to-consumer information in Europe: the blurred margin between promotion and information.	Criteria 1, 2 not met
PubMed	2008	Zikmund-Fisher BJ, Fagerlin A, Roberts TR, Derry HA, Ubel PA.	Alternate methods of framing information about medication side effects: incremental risk versus total risk of occurrence.	Criteria 1, 2 not met
PubMed	2007	Sansgiry SS, Chanda S, Shringarpure GS.	Impact of bilingual product information labels on Spanish-speaking adults' ability to comprehend OTC information	Criteria 1, 2 not met
PubMed	2007	Shrank WH, Agnew-Blais J, Choudhry NK, Wolf MS, Kesselheim AS, Avorn J et al.	The variability and quality of medication container labels.	Criteria 1, 2 not met
PubMed	2007	Vinker S, Eliyahu V, Yaphe J.	The effect of drug information leaflets on patient behavior.	Criteria 2 not met
PubMed	2007	Allen LaPointe NM, Pappas P, Deverka P, Anstrom KJ	Patient receipt and understanding of written information provided with isotretinoin and estrogen prescriptions.	Criteria 2 not met
PubMed	2006	Yoon EY, Davis MM, El Essawi H, Cabana MD.	FDA labeling status of pediatric medications.	Criteria 1, 2 not met
PubMed	2005	Steinmetz KL, Coley KC, Pollock BG.	Assessment of geriatric information on the drug label for commonly prescribed drugs in older people.	Criteria 1, 2 not met
PubMed	2004	Nabors LA, Lehmkuhl HD, Parkins IS, Drury	Reading about over-the-counter medications.	Criteria 2 not met

		AM.		
PubMed	2004	Zineh I, Gerhard T, Aquilante CL, Beitelshees AL, Beasley BN, Hartzema AG.	Availability of pharmacogenomics-based prescribing information in drug package inserts for currently approved drugs.	Criteria 2 not met
PubMed	2004	Oldman M, Moore D, Collins S.	Drug patient information leaflets in anaesthesia: effect on anxiety and patient satisfaction.	Criteria 1, 2 not met
PubMed	2003	Shah SN, Sesti AM, Copley-Merriman K, Plante M.	Quality of life terminology included in package inserts for US approved medications.	Criteria 2 not met
PubMed	2003	Coleman B.	Producing an information leaflet to help patients access high quality drug information on the Internet: a local study.	Criteria 1, 2 not met
PubMed	2003	Mansoor LE, Dowse R.	Effect of pictograms on readability of patient information materials.	Criteria 3 not met
PubMed	2002	van Grootheest AC, Edwards IR.	Labelling and 'Dear Doctor' letters: are they noncommittal?	Criteria 1, 2 not met
PubMed	2000	Levy G, Zamacona MK, Jusko WJ.	Developing compliance instructions for drug labeling.	Criteria 1, 2 not met
PubMed	2000	Jones R, Finlay F, Crouch V, Anderson S.	Drug information leaflets: adolescent and professional perspectives.	Criteria 1, 2 not met
PubMed – update	2012	Yin HS, Parker RM, Wolf MS, Mendelsohn AL, Sanders LM, Vivar KL et al.	Health literacy assessment of labeling of pediatric nonprescription medications: examination of characteristics that may impair parent understanding.	Criteria 1, 2 not met
PubMed - update	2012	Dzioba L, Stanczak A.	Summary of product characteristics (SmPC)—study on utilization of information presented in SmPC by different groups of physicians.	Criteria 2 not met
PubMed PILs BOX	2012	Rahmner PB, Eiermann B, Korkmaz S, Gustafsson LL, Gruven M, Maxwell S et al.	Physicians' reported needs of drug information at point of care in Sweden.	Criteria 2 not met
PubMed PILs BOX	2011	Dowse R, Ramela T, Browne SH.	An illustrated leaflet containing antiretroviral information targeted for low-literate readers: development and evaluation.	Criteria 3 not met
PubMed PILs BOX	2010	Chuang MH, Lin CL, Wang YF, Cham TM.	Development of pictographs depicting medication use instructions for low-literacy	Criteria 3 not met

			medical clinic ambulatory patients.	
PubMed PILs BOX	2007	Shrank W, Avorn J, Rolon C, Shekelle P.	Effect of content and format of prescription drug labels on readability, understanding, and medication use: a systematic review.	Criteria 1, 2 not met
PubMed PILs BOX	2003	Brass EP, Weintraub M.	Label development and the label comprehension study for over-the-counter drugs.	Criteria 1, 2 not met
PubMed PILs BOX	1998	Buck ML.	Providing patients with written medication information.	Criteria 1, 2 not met
PubMed PILs BOX	1998	Morrow DG, Hier CM, Menard WE, Leirer VO.	Icons improve older and younger adults' comprehension of medication information.	Criteria 2 not met
PubMed PILs BOX	1997	Friedman CP, Romeo D, Hinton SS.	Healthcare decisions and product labeling: results of a consumer comprehension study of prototype labeling for proposed over-the-counter cholestyramine.	Criteria 1, 2 not met
Embase PILs BOX	2012	Afolabi MO, Akinwale VO, Akinyemi OA, Irinoye AI.	Patient use and perception of medicine information leaflets.	Criteria 3, 5 not met
Embase PILs BOX	2011	Bailey SC, Schillinger D, Chen A, Sarkar U, Larsen E, Wolf M.	Improving understanding of rx instructions among patients with limited English proficiency.	Criteria 3, 5 not met
Embase PILs BOX	2011	Hogan ME.	Enhancing medication adherence by improving the clarity of labels for prescription drugs.	Criteria 1, 2 not met
Embase PILs BOX	2009	Volpato LF, Martins LC, Mialhe FL.	Medicine information leaflets: Help or hinder the understanding of users?	Criteria not met
Embase PILs BOX	2007	Arguelloa B, Fernandez-Llimosb F.	Professionals' access to drug package inserts.	Criteria 5 not met
Embase PILs BOX	2006	Bansal V, Dhamija P, Medhi B, Pandhi P.	Package inserts-do they have any role?	Criteria 3 not met
Embase PILs BOX	2005	Rollins BL, Sullivan DL.	Evaluating consumer understanding of two patient instructions for use inserts provided by manufacturers.	Criteria 1, 2 not met
Embase PILs BOX	1997	Grisaffe DB, Shellabarger S.	Consumer comprehension of efficacy data in four experimental over-the-counter label conditions.	Criteria 1, 2 not met
Sociological Abstracts	2006	Clerehan R, Buchbinder R.	Toward a more valid account of functional text quality: The	Criteria 2 not met

PILs BOX			case of the patient information leaflet.	
Comm Mass Media Complete PILs BOX	2010	Zethsen KK, Askehave I.	PIL of the month: A studu of best practice in EU patient information leaflets.	Criteria 2 not met
Comm Mass Media Complete PILs BOX	2003	Bower AB, Taylor VA.	Increasing Intention to Comply with Pharmaceutical Product Instructions: An Exploratory Study Investigating the Roles of Frame and Plain Language.	Criteria 1, 2 not met

Appendix 2 Extra tables chapter 4 (open questions)

Stakeholders answers on information currently missing in the PIL which can improve patients' ability to read and understand the PIL

Representatives of patient and consumer organizations*
▪ Use of pictures / pictograms (n=4); ▪ PIL text written with lay language, without using medical terms (n=3); ▪ Inclusion of key information (n=2); ▪ Inclusion of a lexical section, in case medical terms cannot be avoided; ▪ Information for patients who have problems with various allergies; ▪ Information related to (healthy) lifestyles that can improve the condition ▪ Explanation of the reasons why certain advise in the PIL is given in a particular way; ▪ Present adverse effects by incidence; ▪ Summary of the information presented; ▪ Inclusion of benefit information; ▪ Reduce length of the PIL; ▪ Comparative information, e.g.: how does this drug relates to placebo or other medicines used for the same indication.
Representatives of health care providers organizations
▪ Statement mentioning that medicines are complicated and that the leaflet only provides basic information and that HCP can help with the medicine and the PIL; ▪ PILs should be targeted at a reading age of 7; ▪ Pharmacovigilance should be more pointed out. ▪ Information regarding the use of a medicine with other medicine for the most common diseases, such as hypertension etc. ▪ Summary of the information presented; ▪ Harmonised structure; ▪ Inclusion of benefit information.

Stakeholders answers to problems with the PILs, mentioned by stakeholders, divided in content, layout and other problems.

Representatives of patient and consumer organizations (N=44)
Content-related problems: ▪ Too many medical terms (n=5) ▪ Volume of the text; too much text (n=4) ▪ Too many side-effects (n=4) ▪ Overall text complex and hard to understand the message (n=3) ▪ Text difficult to understand for elderly patients (n=3) ▪ Text difficult to understand for low literate patients (n=2) ▪ Instructions of use hard to follow (n=2) ▪ Warning section too extensive (n=1) ▪ Too many interactions and co-medication (n=1) ▪ Contraindication section is hard to follow (n=1) ▪ Mechanism of action not clear (n=1) ▪ Problems with the dosage (n=1) Layout-related problems: ▪ Font too small (n=10) ▪ Hard to read (n=2) ▪ Difficult to find answers (n=1) ▪ Size of the leaflet too long (n=1) ▪ No use of pictures (n=1) ▪ Bad tables / graphs (n=1) Other problems: ▪ Patients not aware to read the PIL (n=1) ▪ PIL not suitable for patients with cognitive problems (n=1) ▪ PIL too sophisticated (n=1) ▪ Confusing leaflets (n=1)
Representatives of health care providers organizations (N=22)
Content-related problems: ▪ Too many medical terms (n=6) ▪ Too many side-effects (n=4) ▪ Too many interactions (n=3) ▪ Instructions of use hard to follow (n=3) ▪ Overall text complex and hard to understand the message (n=2) ▪ Lack of information for the elderly (n=1) ▪ Text difficult to understand for low literate patients (n=1) ▪ Volume of the text; too much text (n=1) ▪ Text is confusing (n=1) Layout-related problems: ▪ Font too small (n=2) ▪ Key-information not highlighted (n=1) Other problems: ▪ Patients do not read the complete PIL (n=1) ▪ PIL too sophisticated (n=1) ▪ Some patients do not have access to the PIL (n=1) ▪ Many patients throw away the PIL (n=1) ▪ Patients do not comply with the instructions in the PIL (n=1) ▪ Do not appreciate the significance of what they read (n=1)
Representatives of pharmaceutical industry (N=107)
Content-related problems: ▪ Too many medical terms (n=37) ▪ Volume of the text; too much text (n=30)

- Too many side-effects (n=19)
- Text too long (n=10)
- Overall text complex and hard to understand the message (n=9)
- Text difficult to understand for low literate patients (n=8)
- Problems with the dosage (n=3) and understanding posology (n=5)
- Instructions of use hard to follow (n=4)
- Warning section too extensive (n=2)
- Contradictory information (n=2)
- Too many interactions and co-medication (n=2)
- Indication of medicine is not clear (n=1)
- Hard to understand duration of treatment (n=1)

Layout-related problems:
- Font too small (n=19)
- Size of the leaflet too long (n=14)
- Difficult to find answers (n=5)
- Bad structure of the PIL (n=5)
- Headlines not clear (n=3)
- Key-information not highlighted (n=2)
- Most recent information not highlighted, making it difficult for chronic patients knowing what is new in the PIL (n=1)

Other problems:
- QRD template (n=9)
- Liability issues (n=9)
- Patients do not read the complete PIL (n=2)
- PILs are difficult to manipulate/handle (n=1)
- Some patients may not have access to PILs (n=1)
- PILs not suitable for blind patients (n=1).
- Representatives of user testing companies (N=6)

Content-related problems:
- Patients of low document skills struggle with words and concepts that are clear to health professionals.
- Older people have difficulty with tables and small text.
- Too much volume of text (meaning only the number of words not deleting of required information).
- Too much template text.
- Ambiguous information.
- The most important information is not in the beginning.
- Too much non-quantifiable phrases and difficult words.

Layout-related problems:
- Length of the PIL.
- Structure of the leaflets. A single template does not suit all patients in all countries, in all 25 languages for all types of medicines.
- The visual design is unattractive and unappealing. There is no relation between the quality of the medicine and the quality of the information.

Other problems:
- Too much associated with the liability law.
- Regulators do not have day-to-day contact with patients, and official solutions or texts are far too complex.

*) if no nr of respondents is mentioned in the table, the suggestion was made by one respondent