

Feasibility and value of a possible “key information section” in patient information leaflets and summaries of product characteristics of medicinal products for human use

The PILS-BOX study

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This study has been financed by the European Union in the frame of the EU Health Programme under the framework Contract N° EAHC/2010/Health/01.

ISBN
DOI

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Executive summary

Background

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

In December 2008 the European Commission tabled legislative proposals set out to strengthen and rationalize pharmacovigilance in the EU. These proposals contained the introduction of new sections in SmPC and the PIL on 'key information' with the objective to allow patients and health care professionals to rapidly identify key safety messages, balanced with information on the benefits of medicines. This proposal of potentially adding a new "key information" section in the SmPC and the PIL, however, was not included in the legislative text which was adopted in 2010 (Directive 2010/84/EU and Regulation (EU) No 1235/2010). The Commission wanted an assessment on the current knowledge on the added value of such section.

Assessment

The objective of this study is to provide the European Commission with an assessment of the current evidence with regard to:

- the potential effects of the introduction of "key information" sections to rapidly identify key safety messages balanced with information on the benefit of medicines in patient information leaflets (PIL) and Summaries of Product Characteristics (SmPC);
- the feasibility of such a tool in the context of the European Union legislation on authorisation of medicinal products for human use and, if possible:.
- to assess the potential cost/efficacy of adding a key information in the context of the EU legislation.

The assessment included an extensive literature search, a European-wide stakeholder survey and a SWOT-analysis (see box on page 8). It should be noted that the evidence found was limited and that the stakeholders – of whom only a minority responded to the survey – hold mixed opinions on the topic. Based upon the assessment we derive three major conclusions.

Conclusion 1: Too early for evidence-based EU-wide introduction of a key information section

The first and main conclusion of this assessment is that, while the number of examples of key information sections seems to be growing, scientific evidence on the added value of a key information section is very limited and is inconclusive so far. This conclusion is based on:

- the lack of evidence found in the scientific literature although the small number of studies have shown no negative findings so far, with users in favour, and on
- the generally mixed opinions different stakeholders have on adding a key information section to PIL and SmPC, how it should look like and what information it should include although there is a divide between patients organisations and health care providers who are more positive about the idea in general, and the pharmaceutical industry and regulators who are more negative.

Evidence is especially limited for key information sections combining risk and benefit information in the PIL: only one study was found. It concluded that the PIL with the key information section was perceived to be as difficult, well designed and useful as a PIL without this section. Yet, participants were enthusiastic about the section and considered it an improvement. Additionally, evidence on including benefit information in patient information shows that this information increases patients' knowledge about the medicine and positively influences their judgment of the medicine. The two studies which included a key information in a revised SmPC found a positive attitude of professionals. Hence there is face value in the use of a key information section in the PIL and SmPC – patients are positive about the idea and, although there is limited evidence about the benefits of such a section, there is no evidence of harm as well. The lack of evidence regarding whether such a section has added value for patient understanding and patient safety, on how such sections should ideally be composed and what information should be included suggests the need for further research, including the cost efficacy of such sections.

Another relevant point to add is that research so far has not covered the point that the two documents (PIL and SmPC) are separate but linked. At present, the PIL is based upon the SmPC, and so a key information section in the latter would shape such a section in the first. But is the information prescribers need in a key information section the same as a patients need? This is not necessarily the case.

Conclusion 2: UK experience offers potential for gathering evidence

Evidence can be built in different ways. The first way is to learn from the UK, as far as we know, the only country in the European Union where key information sections are used. Legal justification for a key information section may come from the provisions of article 62 of Council Directive 2001/83/EC which allows the inclusion of other information which is useful for the patient, consistent with the SmPC and being non-promotional.

The United Kingdom introduced a key information section in a selected number of PILs, following a 2005 Medicines and Healthcare products Regulatory Agency (MHRA) report which suggested including a 'headline section' in patient information leaflets. The UK key information sections are constructed based upon guidelines in this report, which might be useful for deciding on which information to be included in the key information section and how to present this information, as well as design aspects. In the upcoming few years more evidence should be gathered on the added value of these sections in the UK. This evidence may guide potential further developments at the EU-level. The EU could facilitate studies in the UK on scientifically testing the key information section.

Conclusion 3: EU-wide user tests needed to develop standards for key information section

It is not yet clear what information should be included in a key information section. Both the literature and the stakeholder consultation are inconclusive on this, with the exception of risk information. Therefore, in case the EU were to proceed with the introduction of a key information section and wants this section to be evidence-based, user testing on selected PILs and SmPCs across the EU is recommended. Such testing should focus on different types of key information sections, in terms of lay-out and especially in terms of content. Additionally, it should capture whether the information

fits to users' needs and whether or not users read information other than the key information section, for example as guided by cross-referencing.

Recommendations to the European Commission

Based upon the above the following recommendations are made:

1. Do not introduce a key information section as a mandatory requirement, bearing in mind the current level of evidence.
2. Allow the use of key information sections in PILs which have been user tested with a particular focus on the key information section. This will help gather more evidence on what such section should look like and what information it should include.

In order to further facilitate an introduction of such a section in the future, the following recommendations are made:

3. Retrieve and stimulate evidence from the implementation of headline sections in the UK.
4. Facilitate EU-wide evaluation of a variety of key information sections, preferably on high risk medicines, on selected PILs and SmPCs, through user testing and wider research.
5. Develop criteria for the inclusion of points of information in these sections based upon further surveying of the stakeholders (primarily patients and health professionals) and the outcome of the above testing.
6. Explore the development and impact of key information sections first in electronic versions of the PIL and SmPC.

Methods used in the assessment

Existing evidence of adding a key information section

Collection of existing evidence on the inclusion of a key information section 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 23 articles in international journals and 3 reports.

European wide stakeholder consultation

The following stakeholder groups were consulted through an online structured questionnaire: Patient and consumer organizations (n=46), Health care provider organizations (n=12), pharmaceutical industry (n=40), regulatory officers (n=16) and communication experts (n=8). Participants represented a wide variety of countries in the EU, with an overrepresentation for the UK, the Netherlands, Sweden and Belgium. Afterwards 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 have different interests to other groups in relation to a key information section.

SWOT analysis

The SWOT-analysis presents the strengths and weaknesses of adding a key information section for the safety and efficacy of medicines' use. The SWOT analysis was drafted by the whole research team and was based upon the results from the literature, the stakeholder consultation and the online discussion forum.

Introduction

1.1 Background

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 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 authorized by competent authorities of the Member States (in accordance with *Directive 2001/83/EC*)¹ or by the European Commission (in accordance with *Regulation No 726/2004*) 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 European Medicines Agency or national competent authorities before marketing is authorized. As such, the SmPC and the PIL form an intrinsic part of the authorization process.

Summary of Product Characteristics

The SmPC includes the definitive description of a medicinal product both in terms of its properties (chemical, pharmacological etcetera) and how the product is 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, and it is incorporated in other information sources aimed at health care professionals, such as national information databases. The EU provides a guideline for applicants on how to compose the SmPC document ². Once the medicinal product is approved the SmPC cannot be changed except when the competent authority approves such changes.

Patient Information Leaflets

The PIL is an important source of information for patients. 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 in a safe and appropriate manner. It should also be available upon request for the blind and partially-sighted (*Directive 2001/83/EC, article 56; 56a*). The information on the PIL should reflect the results of consultations with patients from the target group (*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 market 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 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).

¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20091005:EN:PDF>

² http://ec.europa.eu/health/files/eudralex/vol-2/c/SmPCguidrev1-oct2005_en.pdf

While efforts have been made at the EU level to improve the information provided in the PIL, there has been considerable criticism. This criticism includes that PILs are hard to read and understand (1). Several studies on PILs support this criticism (2;3). Readers encounter problems in finding the right information (3). Dixon-Woods argues that the reason for PILs not being easily understood, may be that the focus is too much on the concept of readability. 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 (4). A systematic review found that most people did not value the written information they received, with concerns about complex language and poor visual presentation. In addition, patients valued information that contained a balance of harm and benefit information (5). For communication to be effective the information should be noticed, read, understood, believed and remembered. When this goal is not reached for the PIL this may have negative consequences, such as non-adherence to medication because of misinterpretation of the risk of side-effects. Vulnerable groups are especially at risk from these failures, as it is very hard to fulfil all criteria for effective (written) communication for these groups. One way that has been suggested to improve the readability of the PIL for all patient groups is adding a section with so-called key information to the PIL.

1.2 Key information sections

In the United Kingdom, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has suggested including a 'headline section' in patient information leaflets, which should provide an overview of the key information related to the safe and effective use of the medicine (1). Such a section was said to be potentially useful and feasible in highlighting information to increase safety and enhance efficacy of the uses of medicines in both the PIL and the SmPC. Adding a key information section potentially may have an added value because many leaflets are lengthy due to the complexity of the SmPC they are based upon, and they may be poorly laid out. As a result, patients or health professionals may quickly lose interest in the document, failing to read or understand information crucial to the safe use of the medicine. The report of the committee instituted by MHRA included an example of a key information section, which was called a 'headline section'. This was described as information presented prominently at the beginning of a PIL, summarising a few key messages for safe and effective use. The report included two examples of a headline section (for carbamazepine and ciprofloxacin). Since then, a number of UK PILs have a headline section, some on the request of the UK regulator, the MHRA.³ The legal justification given for including such a section is from the provisions of article 62 of Council Directive 2001/83/EC which allows the inclusion of other information which is useful for the patient, consistent with the SmPC and being non- promotional.

The United States and Australia also have information boxes that can be considered as key information sections (6) but those differ from those in the UK as they only focus on warning for serious adverse effects. In the US, both prescription and Over The Counter (OTC) medicines can have a boxed warning (also called 'black box' warning). The Food and Drug Administration (FDA) can require a pharmaceutical company to place such warning on the PIL of a prescription drug. The addition of such a box

³ <http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con030906.pdf>
<http://www.mhra.gov.uk/home/groups/pl-a/documents/regulatorynews/con068247.pdf>

implies that medical studies indicate that the medicine carries a significant risk of serious adverse effects. It is the strongest warning the FDA can require. These boxed warnings are included in both the Product Information (PI; equivalent to the EU SmPC) and the patient information. The number of medicines containing a boxed warning section is much higher in the US compared to Australia (6). While in the US there are at least 400 medicines with a boxed warning, Buckley estimates that this is at least less than a quarter of this (so 100) in Australia. Moreover, US boxed warnings are considerably longer than in Australia, up to 10 times as long. Yet, Australian text boxes clearly describe what a prescriber has to do. Within the US the information provided in boxed warnings also varies considerably (7) and, even for same-class drugs, warnings can be different (8). It is important to note that such boxed warnings focus on a particular safety issue, and are not a balanced summary of risks and benefits as was proposed in the non-adopted EU proposals (see section 1.3 below).

Another US development related to a key information section in PILs is the Drug Facts Box. This is a summary of information for over-the-counter products which is now mandated to be included on the medicine pack. This box has a standardized format and content requirements to assist consumers to read and understand the information, to allow them to use the products safely and effectively. In 2013, the Australian Government consulted on the introduction of a similar box (called the Medicines Information Box) for over-the-counter products.

1.3 Adding a key information section to PIL and SmPC in the EU?

In December 2008 legislative proposals were set out to strengthen and rationalize pharmacovigilance in the EU. These proposals contained several provisions related to the content of SmPC and PIL. One of which contained the introduction of new sections in SmPC and the PIL on 'key information' with the objective to allow patients and health care professionals to rapidly identify key safety messages, balanced with information on the benefits of medicines. The recitals of the Commission proposal read as follows: *"(10) In order to make it possible for the healthcare professionals and patients to identify easily the most relevant information about the medicines they use, the summary of the product characteristics and the package leaflet should include a concise section on the key information about the medicinal product and information how to minimize its risks and maximize its benefits."* This proposal of potentially adding a new "key information" section in the SmPC and the PIL, however, was not included in the legislative text which was adopted in 2010 (*Directive 2010/84/EU and Regulation (EU) No 1235/2010*). An assessment on its possible added value was required. **Chapter 2 includes a more detailed description of the legal context.**

1.4 Objectives

This report provides an assessment of the possible added value of a key information section to the PIL and SmPC. Such key information sections would not only have to include warnings, but also present the main benefits of the medication as well.⁴ As such, this PIL-S BOX study had the following aims:

- to collect existing evidence on the potential impact of adding a key information section on the safety and efficacy of medicines' use;
- to assess the feasibility of adding a key information section in the context of the EU legislation;

⁴ The revised QRD template published in July 2011 included specific guidance inviting companies to include, under section 1 of the PIL, information on the benefits of the medicine which is compatible with the SmPC and of non-promotional nature.

-
- to assess the potential cost/efficacy of adding a key information in the context of the EU legislation.

1.5 Work packages

The PIL-S BOX study included three work packages, each one with their own focus.

1.5.1 WP1: Existing evidence of adding a key information section

WP1 focuses on collecting existing evidence on the inclusion of a key information section in the PIL and SmPC and on the feasibility and cost/efficacy of including such section within the boundaries of EU legislation. By "cost/efficacy" it is meant the impact of the inclusion of key information sections in both PILs and SmPCs on the use of medicines related to the costs of such implementation. With regard to both the PIL and the SmPC the following questions were investigated:

- What evidence is available in and outside Europe on the inclusion of a key information section with regard to the safety and efficacy of medicines' use?
- What information can be identified as 'key' information for a special section in the PIL and SmPC from the literature?
- Given this evidence and given EU legislation: how feasible is it to include such key information section and what is the cost efficacy of including such key information section?

Chapter 3 describes the results of these search for existing evidence.

1.5.2 WP2: Stakeholder consultation

WP2 focused on the opinions of relevant stakeholders such as professional organisations, patient and consumer organisations, regulatory offices and pharmaceutical companies. The following research questions were asked to stakeholders in the EU:

- What information can be identified as 'key' information for a special section in the PIL and SmPC according to the stakeholders?
- What are the challenges of adding a key information section in PIL and SmPC so that it is both scientifically valid and as well provides additional value for patients (PIL) and health care professionals (SmPC) in terms of faster and easier identification of the necessary key information?
- What changes does the addition of a key information section entail in terms of EU legislation?
- What are the positive and negative effects of key information section in PIL and SmPC and their value for their respective users?
- What are potential alternatives for a key information section? What are the advantages and disadvantages of each alternative?

Chapter 4 includes the results of this stakeholder consultation.

1.5.3. WP3: SWOT analysis

The last WP provided a SWOT analysis of the potential introduction of a key information section. This SWOT-analysis presented the strengths and weaknesses of adding a key information section for the safety and efficacy for medicines' use, taking into account positive and negative aspects identified by the literature search and the stakeholder consultation and their relevance in the EU context and also the factors relevant for the cost/efficacy appraisal as found in the literature.

Chapter 5 describes the SWOT-analysis while a general summary including conclusion, discussion and recommendations is provided in chapter 6.

Chapter 2

Legal framework

2.1 Introduction

All medicinal products that are authorized 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. This chapter describes the legal framework regarding PILs and SmPCs within the context of the European Union from 2001 onwards. Although the adding of a key information section is not included in the legislation and in guidelines so far, it is important to describe the legal context in order to see whether and where the key information section would fit in.

2.2 Directive 2001/83/EC

2.2.1 General

Directive 2001/83/EC of the European Parliament and of the Council relating to medicinal products for human use came into force on November 6 2001. This Directive 2001/83/EC was amended several times. The 2010 revision (*Directive 2010/84/EU*) referring to pharmacovigilance is important for this study even though the proposal to add a key information section to the PIL and SmPC was not included in this amendment (see chapter 1). The last consolidated version of Directive 2001/83/EC stems from November 16, 2012 and takes into account the amendments of Directive 2012/26/EU (<http://ec.europa.eu/health/documents/eudralex/vol-1/>). This version was used for the description provided below.

2.2.2 Directive 2001/83/EC on the Summary of Product Characteristics

The recitals of Directive 2001/83/EC read 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 authorization to place a medicinal product on the market a summary of product characteristics (SmPC) should be provided (article 8j). The SmPC has to be in accordance with article 11 of the Directive (see Box 2.1).

⁵ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20091005:EN:PDF>

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 standardized 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).

2.2.3 Directive 2001/83/EC on the Patient Information Leaflet / Package Leaflet

The recitals of Directive 2001/83/EC read 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). In Title III of the Directive, Placing on the Market, it says that in order to obtain an authorization to place a medicinal product on the market a package leaflet should be provided (article 8j). Also in Annex 1 of the Directive it reads that a proposed package leaflet should be part of the marketing authorization dossier (section 1.3.2.). This package leaflet has to be in accordance with article 59 of the Directive (see below).

Requirements for package leaflets

Title V of Directive 2001/83/EC, 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 summary of product characteristics. 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 in with the particulars listed in the SmpC the competent authority has to refuse to grant the marketing authorization (article 61.2).

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 pharmacotherapeutic 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.

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.⁶ Article 62 allows for the inclusion of other information which is useful for the patient, consistent with the SmPC and being non-promotional. And Article 56a states that marketing authorisation holders have to ensure that the package information leaflet is made available in request from patients 'organizations for the blind and partially-sighted. In addition to the provisions in article 59(1) concerning content and order of the PIL article 59(3) requires applicants to provide evidence that the leaflet proposed for marketing reflects the results of consultation with target patient groups (see section 2.4).

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.

⁶ There are some exceptions for this, for example for certain orphan medicinal products

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

1. A guideline on Summary of Product Characteristics (SmPC) – September 2009⁷

This guideline 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 what information has to be addressed in that particular section, more practical advices can be found in the templates of the Quality Review of Documents group (QRD).

2. Guideline on the packaging information of medical products for human use authorised by the community (latest update July 2013)⁸

This guideline has been prepared in order to describe how the provisions of Directive 2011/83/EC apply in the case of an authorisation to granted by the Community in case of a centralized marketing authorization process.

3. Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, January 2009)⁹

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 authorization holders in preparing the package leaflet and advices 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 to test the package leaflet (see section 2.4).

2.4 User testing

One way to consult patients to comply with the legislation is through user-testing of the package leaflet. The Readability Guideline says that 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."(p. 20) By testing, problem areas in leaflets can be identified and improved accordingly. When user testing, the use of a full mock-up of the leaflet in the paper, colours and style as used for the leaflet in the marketed pack is required (including 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.

User testing has only to be done in one of the official languages 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. When approving the leaflet, the

⁷ ec.europa.eu/health/.../smpc_guideline_rev2_en.pdf

⁸ ec.europa.eu/health/files/.../bluebox_06_2013_en.pdf

⁹ http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf

competent authorities will look for evidence that patients who need the information can understand it and act appropriately based on this information.

2.5 Adding a key information section

As stated in Chapter 1, the issue of adding a key information section to PILs and SmPCs in the EU became relevant after the Commission tabled in December 2008 legislative proposals set out to strengthen and rationalize pharmacovigilance in the EU. The 2008 legislative proposals contained among other proposals the introduction of new sections in SmPC and the PIL on 'key information 'with the objective to allow patients and health care professionals to rapidly identify key safety messages, balanced with information on the benefits of medicines" . This proposal of potentially adding a new "key information" section in the SmPC and the PIL, however, was not included in the legislative text which was eventually adopted in 2010 (Directive 2010/84/EU and Regulation (EU) No 1235/2010).

Chapter 3

Literature study

This chapter presents the literature search that has been conducted to collect existing evidence on the inclusion of a key information section in the PIL and SmPC as well as on the feasibility and cost-efficacy of including such section within the boundaries of EU legislation. The first paragraph describes the methodology used for the literature study. The results are presented in paragraph 3.2.

3.1 Methods

3.1.1 Search for scientific literature

Search strategy

A comprehensive literature search was conducted in the following electronic databases: PubMed, Embase, Sociological Abstracts and Communication and Mass Media Complete.

The search string used for PubMed was:

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((("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 "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])10
```

The following restrictions were applied: publication date 1995-now, 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. These electronic searches were supplemented by manual searching of reference lists of relevant articles and citation tracking of relevant articles ("snowball method").

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 and includes information on a key information section or potential alternatives;
2. The publication refers to the evidence with regard to subjects to be included in a key information section, the safety and efficacy of medicines' use, the feasibility of the inclusion of a key information section (including success factors as well as potential negative consequences of a key information section and/or cost efficacy);
3. In case a publication is not in one of the four main languages of the EU (English, German, French or Spanish) or in a language mastered by the

¹⁰ Our strategy was to use a broad search strategy in order not to miss studies. Searches using terms such as headline sections resulted in very little hits.

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- research team (Dutch, Portuguese), it needs to contain a summary (which can be translated in English);
4. 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, MV and LvD, independent from each other. As a 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 abovementioned criteria were applied to these full texts to determine whether the articles were relevant for inclusion in our study.

Data extraction

One reviewer, MV, extracted the following study characteristics of each article:

- General information (first author, year of publication, country)
- Objective of the study
- Involved (type of) medication
- Information included in the key information section
- Evidence for safety and efficacy of medicines' use / feasibility of including a key information section (incl. success factors, negative consequences and/or cost efficacy)
- Authors' conclusions

3.1.2 Search for grey literature

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. In addition, the following relevant websites were searched for relevant documents:

- a) EU/EC websites;
- b) EMA website;
- c) Websites of national ministries of health of the Member States (where available);
- d) Websites of national regulatory offices of the Member States. In addition, all national regulatory offices will be contacted by email asking for relevant references/publications;
- e) Websites of National institutes for safe use of medicines (where available).

3.2 Results

3.2.1 Scientific literature

The search in the electronic databases resulted in a total of 10,068 hits, of which 7,016 were unique. Screening of titles by MV and LvD resulted in a total of 339 potentially relevant titles. Subsequent screening of the corresponding abstracts by the same reviewers yielded 39 abstracts that were potentially relevant for this study, of which full texts were obtained (Table 1). 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 1.

Table 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 ¹	Relevant abstracts ¹	Relevant abstracts PIL-s BOX
PubMed	5,019	5,019	264	88	33
Embase	4,660	1,644*	56	24	5
Sociological Abstracts	294	275	3	1	0
Communication and Mass Media Complete	95	78	16	6	1
<i>Total</i>	<i>10,068</i>	<i>7,016</i>	<i>339</i>	<i>119</i>	<i>39</i>

* Embase is known to show a large overlap with PubMed (both cover MEDLINE records)

¹ includes potentially relevant abstracts for both the PIL-s project (Van Dijk et al 2013) and PILs-BOX project

The snowball method provided three additional relevant studies. Moreover, over the course of this literature review, a new study was published by one of the project team members (TR). As this was the only study on headline sections in SmPCs so far, we decided to include this study as well. Ultimately, a total of 23 studies met all inclusion criteria and were included.

Description of the studies

Table 2 presents the main characteristics of the 22 included studies:

- One study that evaluated the influence of including a 'headline section' in the PIL (9)
- One study on user testing study of two SmPCs which included headline sections (10) and a further study used the results of focus groups with doctors to create a revised SmPC format which included a 'synopsis' (11).
- Four studies examined the impact of including benefit information in the PIL (12-15),
- Sixteen studies investigated the consequences of the 'Black Box Warning' (BBW) on prescriber compliance and/or medication use (16-31).

Headline section

The study of Dolk et al. (2011) user tested a headline section in the PIL for the anticonvulsant carbamazepine as proposed by the MHRA in its report "Always read the

leaflet” (1) (see Box 3.1). The influence of including this section on the ‘findability’ and comprehension of information and perception of the design of the leaflet was evaluated (9). They concluded that the headline section did not influence ‘findability’ or comprehension of information in the PIL. Furthermore, the PIL with the headline section was perceived to be as difficult, well designed and useful as a PIL without this section. However, the interviews showed that participants were enthusiastic about the section and thought it was an improvement to the PIL.

Box 3.1: Headline section in PIL for carbamazepine evaluated by Dolk et al., 2011 (9).

Important things that you need to know:

- Carbamazepine tablets are prescribed for different illnesses including epilepsy, mental health problems and trigeminal neuralgia.
- **Take Carbamazepine regularly to get the most benefit.** Do not stop taking the medicine without talking to your doctor. Sometimes stopping the medicine can cause problems.
- Carbamazepine can cause side effects; although most people do not have serious problems (see section 4 for details). If you have high temperature, sore throat, skin rashes or skin yellowing, mouth ulcers, bruising or bleeding, stop taking Carbamazepine and see your doctor straight away.
- Some side effects may happen early in treatment (such as feeling dizzy, tired or clumsy). These often go away after a few days as your body gets used to the medicine.
- Taking other medicines may sometimes cause problems (see section 2 for details). Check with your doctor or pharmacist before taking any other medicines.
- Talk to your doctor if you are pregnant, or might get pregnant while taking Carbamazepine. This is because it can harm the baby.

Now read the rest of this leaflet - it includes other important information on how to use this medicine safely and effectively.

This leaflet was last updated on 08 February 2008

'User testing of SmPCs with headline section'

The study of Raynor et al user tested two SmPCs – one with general practitioners and one with senior hospital doctors - to assess the effectiveness of the SmPC and communicating essential information to prescribers (10). They followed the usual iterative process with user testing over 5 rounds – the number of points of information meeting the target rose from 6/15 in the first document tested, to 11/15 in the final revised version. The latter version included a 'Key information' section (see Box 3.2). Qualitative responses showed that SmPCs have a low perceived value to doctors' prescribing behaviour. One participant testing the original SmPC said '*Points should perhaps be aggregated on the front page*' and responding to the revised SmPC with the Key information section on front page, another said '*That's useful, the front page...*'.

Box 3.2 Headline section in SmPC for CellCept evaluated by Raynor et al 2013

Key information

- CellCept is used with ciclosporin and corticosteroids to prevent acute transplant rejection in patients with allogeneic renal, cardiac or hepatic transplants.
- Start CellCept within 72 hours of renal and 5 days of cardiac transplants. Give IV CellCept for the first 4 days after hepatic transplant, then start CellCept as soon as it can be tolerated. See Section 3 for the dose regimes.
- CellCept interacts with some other medicines, including some other anti-rejection drugs, anti-virals and antibiotics. Use with azathioprine is not recommended.
- Vaccines may be less effective during treatment - in particular, avoid live attenuated vaccines (see Section 4.2 – Special warnings: "Vaccinations").
- CellCept should not normally be used during pregnancy - obtain a negative pregnancy test before treatment. Women should use effective contraception before, during and after treatment, and talk to their doctor straight away if they become pregnant. Breast-feeding is contra-indicated (see Section 4.4 – Pregnancy, Fertility and Lactation).
- The main side effects from co-administration of CellCept with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting.
- CellCept can cause bone marrow suppression. Tell patients to report immediately any sign of infection, unexpected bruising or bleeding. Take regular full blood counts (for frequency of blood counts and other information, see Section 4.2 - Special warnings: "Bone marrow suppression and neutropenia").
- Patients having immuno-suppressive regimens including CellCept are at increased risk of lymphomas and other malignancies (particularly skin).
- If renal function deteriorates or the patient gets neurological symptoms, consider a differential diagnosis of opportunistic infection in immune-suppressed patients.

See over for the full information about CellCept

Revised SmPC format with a 'synopsis' resulting from focus groups with doctors
 The study of Vromans et al (2013) used the results of focus groups with German doctors to create a 'more user-friendly' SmPC (11). The revised SmPC included additional sections including a section at the beginning which was variously described as a 'synopsis', 'summary' and 'brief summary'. The revised SmPC was then tested in an online quantitative survey of German doctors which found that 73% said they found the 'brief summary' useful or very useful and 74% user-friendly or very user friendly.

SUMMARY OF PRODUCT CHARACTERISTICS /SmPC)	
Simvastatin Film-Coated Tablets	
Information on the Medicinal Product "Simvastatin Film-Coated Tablets"	
Active substance	Simvastatin
Pharmacotherapeutic group	HMG-CoA reductase inhibitor, cholesterol reducer
Indication	Hypercholesterolaemia, CHD prevention
Contraindications	<ul style="list-style-type: none"> • Hypersensitivity to simvastatin or to any of the excipients. • Active liver disease or unexplained persistent elevations of serum transaminases. • Pregnancy and lactation. • Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors (e.g. nelfinavir), erythromycin, clarithromycin, telithromycin and nefazodone). • Concomitant administration of gemfibrozil, ciclosporin or danazol.
Pharmaceutical form(s)	Film-coated tablets Simvastatin 5 mg film-coated tablets Simvastatin 10 mg film-coated tablets Simvastatin 20 mg film-coated tablets – scored, divisible Simvastatin 40 mg film-coated tablets
Method of administration / posology	Oral administration Once a day in the evening. Dosage range: 5–80mg. Adjustments of dosage in intervals of 4 weeks.
Effects	<ul style="list-style-type: none"> • Significant reduction of the LDL cholesterol level • Significant reduction of apolipoprotein B • Moderate increase in HDL • Reduction of triglycerides • Reduction in the LDL/HDL ratio
Safety	Safety has been documented in clinical long-term studies with up to approx. 30,000 patients The following serious undesired effects have been documented: <ul style="list-style-type: none"> • Rhabdomyolysis / myalgia, increase in CK value • Increase in serum transaminases

Benefit information

One study from Belgium investigated the impact of including benefit messages in patient package inserts on patients' knowledge about medicines and their benefit versus risk perception (12). They studied three types of benefit messages: one that focused on explaining the drug's action, one focused on monitoring signs of healing, and one explained the relation between the nature of the disease and the drug's action (see Box 3.3). Their results showed that inclusion of these benefit messages increased patients' knowledge about medication. In addition, more patients rated the benefit of the medicine higher than the risk.

Box 3.3: Benefit messages evaluated by VanderStichele et al. 2002 (12).

Benefit message exp. 1: In normal digestion ingested food flows in one direction from the mouth to the stomach and then to the digestive tube. Little muscles at the entrance and at the exit of the stomach keeps the food from flowing back. Other muscles insides the stomach and in the intestines mould the food and push it further. [Cisapride] helps these little muscles to work well together. This favours good digestion.

Benefit message exp. 2: A fungus can cause infection of one or more toenails. [Itraconazol] stops the growth of the fungus and kills it. Once the fungus is killed by [itraconazol], a healthy nail will grow back. The healing process takes time. Therefore, the signs of infection can still be present for a while. It can take several months before the nail looks completely healthy.

Benefit message exp. 3: Psychosis is a mental disease, in which the working of he brain is disturbed as to thinking, feeling and acting. The symptoms can be: confusion, hallucinations, distortions in hearing and sight, paranoia, feelings of anxiety and tension. [Risperidon] relieves the symptoms of chronic psychosis, and helps to restore normal social function in society. It is often necessary to take the medicine continuously for a long time to suppress the signs of the disease. When treatment is stopped, symptoms can return.

Two studies from the UK examined the impact of adding different benefit statements on patients' ratings of e.g. satisfaction with the information, perceived risk of the medication, effectiveness of the medication, and intention to comply (13;14). In the first study, Berry et al. (2002) conducted three experiments, one of which involved adding a positive benefit statement which read: "Epidoxin has been shown to be very effective. The symptoms of your disease would clear in about three or four days". Results from this experiment indicated that this statement led to higher ratings of satisfaction with the information. No effect was found on patients' ratings for perceived risk to health of the medicine or their intention to comply (13). The second study from Bersellini & Berry built on these previous results, and also performed three experiments with adding benefit information (14). Experiment 1 added a statement on the drug's effectiveness (based on the statement used in their previous study), experiment 2 added a statement on the rationale for how the medicine works besides the effectiveness of the drug (based on that used in exp. 1 and by VanderStichele et al. (2002)), and experiment 3 combined both statements with adding a list of four side effects of the medication. All three experiments showed that inclusion of a benefit statement resulted in an improvement of patients' judgement about the medicine (e.g. effectiveness of the medicine, its benefit to health, their satisfaction with the information) (14). Finally, the fourth study by Hamrosi et al (2012) explored patients' opinions about the inclusion of benefit information in the PIL, and focused on textual versus numerical information. This study showed that most participants preferred textual benefit statements, whereas only a small number of participants were in favour of including numerical benefit information (such as the numbers needed to treat). Participants expressed that comprehensive medicine information (both benefits and harms) should be available to support them in their decisions about their medicines (15).

Black Box Warnings

BBWs are issued in the US by the Food and Drug Administration (FDA) and are designed to call attention to serious or even life-threatening risks of the drug in question. One of the following situations is highlighted within a BBW (cited from the FDA's Guidance for Industry, 2011 (32)):

1. There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug; OR
2. There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); OR
3. FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g. under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).

BBWs are the strongest warnings the FDA issues. The text of the warning is usually surrounded by a black border, hence the name. The FDA requires pharmaceutical companies to add the BBW to a prescription drug's label or package insert. The BBW is usually just one of the many tools that the FDA uses for communication about risks. Therefore, it is difficult to investigate the single effect of the BBW on prescribing behaviour or on medication use. However, it can be seen as a type of key information, albeit only addressing the negative side effects of a drug.

In eight studies, the BBW concerned antidepressant use in children and adolescents (16-23), in one study atomoxetine use for the treatment of Attention-Deficit / Hyperactivity Disorder (ADHD) (24), in two studies (atypical) antipsychotics use in elderly patients with dementia (25;26), and in one study the use of droperidol in the management of (postoperative) nausea and vomiting (27). Three studies had a larger scope; they investigated the compliance with BBWs for several medicines regarding the drug-drug, drug-disease and drug-monitoring warnings (28-30).

- **BBW for antidepressant use in paediatric patients**

The BBW highlighted the increased risk of suicidality in paediatric patients for all antidepressant drugs. Five studies were conducted in the USA (19;20;22;23) of which one compared the results with data from the Netherlands (16), two in Canada (17;18) and one in Finland (21). The US studies all revealed significant declines in antidepressant use among paediatric patients after the BBW. In the Netherlands, this decline was also visible. On the other hand, one study in Canada only found an influence of the specific warning issued in the UK in contrast to the generalized warnings issued in the USA and Canada (17). The other study from Canada investigated changes in prescribing by surveying paediatricians and found that 72% of them were aware of the BBW and of these paediatricians 80% changed their prescribing practices (18). Contrary to these studies, the study from Finland found that the overall incidence of antidepressant use among children and adolescents continued to increase after the BBW was issued (21).

- **BBW for atomoxetine use in children and adolescents with ADHD**

The BBW highlighted an increased risk of suicidal thinking in children and adolescents being treated with atomoxetine. Du et al. (2012) examined whether atomoxetine use patterns changed after the BBW. They revealed that incidence rates already

significantly declined in all age groups before the BBW was issued. Therefore, no significant change was found in atomoxetine use after the BBW.

- BBW for antipsychotic use in elderly with dementia-related psychosis

The BBW highlighted the increased mortality among elderly patients with dementia-related psychoses treated with antipsychotic medication. Two studies, both conducted in the US, investigated the impact of this BBW. One study demonstrated a significant decrease in the use of antipsychotics among elderly patients with dementia after the BBW (25). The other study surveyed directors of nursing homes on their practice and found that antipsychotic medications are still widely used in nursing home setting in spite of the BBW as only 40% reduced the usage of these medications after the BBW (26).

- BBW for droperidol use

One study examined changes as a result of the BBW for droperidol which included concerns of serious cardiac arrhythmias (27). A survey was used to study changes in the practice of members of the society of ambulatory anesthesia (SAMBA) as a result of the BBW. A significant decline in the use of droperidol after the BBW was observed; however, more than 90% of respondents of SAMBA did not believe the BBW was justified.

- Prescriber compliance with BBW medication

Lasser et al. (2006) showed that of all outpatients, only few (1%) received a prescription in violation of the BBW. They were most often at risk for drug-disease interactions (91%), followed by drug-laboratory interaction (27%) and drug-drug interaction (3%) (28). Another study, however, found much lower prescriber compliance with BBW recommendations concerning monitoring and contraindications in ambulatory care patients (29). The third study on this topic also showed low prescriber compliance rates with BBWs in ambulatory care patients aged over 65 (30).

Finally, the article of Matlock et al. (2011) provides seven recommendations to potentially improve the application of the BBW so that they might be more helpful to clinicians (31). These are listed in box 3.4.

Box 3.4 Recommendations from Matlock et al on improving the application of the BBW (31)

1. Provide an estimate of the incidence for an adverse drug event, including associated drug doses.
2. Create and publish reasonable standards to define a threshold for boxed warnings (using clinical and incidence criteria). For example, a boxed warning may be considered for less serious effects when the incidence is relatively higher.
3. Strengthen and enforce the systems of post-marketing surveillance and clinical studies, and assignment of causality.
4. Utilize existing established toxic-oriented databases (such as the National Poison Data System) to identify and monitor such issues.
5. Consider an integrated and balanced approach to generating boxed warnings including the safety and availability of alternative therapies, projected effects on prescribing habits, efficacy/benefit of the drug and medicolegal implications.
6. Report a threshold dose, if known, for a particular adverse drug reaction.
7. Institute a graded level of boxed warning, similar to pregnancy drug labeling, which would reflect the quality of data regarding harm and provide some sense of risk to providers.

Taken from Matlock et al. (2011)(31)

Author, year, country	Objective of study	Involved (type of) medication	Information included in key information section	Evidence for safety & efficacy / feasibility (incl. success factors, potential negative consequences, cost efficacy)	Authors' conclusions
Headline section in PIL					
Dolk et al., 2011 (9), UK/ Netherlands	To evaluate influence of a headline section on 'findability' and comprehensibility of information, perception of the leaflet design.	PIL for anticonvulsant carbamazepine	What medicine is for, emphasis on regular taking (not stopping), potential side effects, interaction/contraindication, pregnancy warning (see Box 3.1 for exact text).	No negative or positive effect of headline section on 'findability' and comprehensibility of information. Equal amount of time needed to find correct part of leaflet. Participants did not frequently turn to headline section to answer questions. PIL with headline section was perceived to be as difficult, well designed and useful as PIL without section.	Headline section did not influence 'findability' and comprehensibility of information, but was perceived as an improvement. The latter came from the qualitative part of the user testing process, where participants are asked for their general impressions.
User testing of SmPCs with headline sections					
Raynor et al 2013 UK	To understand the effectiveness of the SmPC document in communicating essential information to doctors.	SmPCs for Lariam (mefloquine for malaria prevention) – tested with GPs and CellCept (mycophenolate an immune-suppressant) – tested with senior hospital doctors.	Summary of the most important points of information. The bulleted information included cross-references to the relevant sections in the SmPC	Qualitative feedback from the doctors found that one of the most likely uses for SmPCs was as a quick reference document, highlighting the importance of information being easy to find and understand. The senior hospital doctors said the 'front page summary' along with other changes, had the most significant impact on their ability to find and understand information.	The key general recommendations included: <ul style="list-style-type: none"> - Add a key information section to the start of the document.
Revised SmPC format with a 'synopsis' resulting from focus groups with doctors					
Vromans et al 2013 Germany	To establish, in the context of the revised European Pharmacovigilance Directive and based on physicians' perspectives, how SmPCs could be more user friendly and better support physicians' interactions with patients, thereby improving patients' own understanding of their medicines	SmPC for simvastatin	Active substance, pharmacotherapeutic group, indication, contraindications, pharmaceutical forms, method of administration/posology, effects, safety. Presented in a two column tabular format	In an online quantitative survey, the 'brief summary' in revised SmPC was said by German doctors to be useful or very useful (73%) and user-friendly or very user friendly (74%).	The introduction of a new section for quick orientation ('synopsis', page 1) ... attested to the alternative SmPC for better comprehension and usefulness.

Benefit information in PIL					
Vander Stichele et al., 2002 (12), Belgium	To explore the impact of including a benefit message in a patient package insert on knowledge about medicines and on subjective benefit/risk perception.	Three PILs: cisapride (exp.1), itraconazol (exp.2), risperidon (exp.3)	Three experiments in which a benefit paragraph focused either on: 1) explaining drug action, 2) monitoring signs of healing, 3) explaining the relation between nature of the disease and drug action (see Box 3.2 for exact text).	The provision of inserts increased the knowledge about medication in all the intervention groups. The scores on the knowledge test were low in the control 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.	Based on these findings, a hypothesis for further research is formulated: 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.
Berry et al., 2002 (13), UK	<i>Three experiments; only exp. 2 investigated benefit information.</i> Exp.2: to examine whether inclusion of benefit information offsets the adverse effect of information about side effects of medication prescribed for severe or mild diseases.	PIL for epidoxin	Exp.2: Positive benefit statement read "... has been shown to be very effective. The symptoms of your disease would clear in about three or four days". Unknown benefit statement read "... is a relatively new drug and its effectiveness has not yet been fully established".	Exp.2: Significantly higher ratings for <i>satisfaction with the information</i> for the positive benefit statement than either the unknown benefit statement or no information. Significantly higher ratings of <i>perceived risk</i> with the unknown benefit statement than the positive benefit statement or no information. Significantly lower ratings of <i>intention to comply</i> with the unknown benefit statement than with either the positive benefit statement or no information.	Providing people with a statement about the positive benefit of taking the medication had relatively little effect on their judgments of perceived risk and intention to comply, whereas informing them that the medication was relatively new and that its effectiveness had not yet been fully established had a negative effect on these ratings.
Bersellini & Berry (14), 2007, UK	To systematically assess the effects of adding information about medication benefits to a short written explanation about a medicine (three experiments).	A (hypothetical) short course antibiotic for either a throat infection or pneumonia	Exp.1: benefit statement about drug's effectiveness added. Exp.2: benefit statement about drug's effectiveness and rationale for how the medicine works added. Exp.3: providing both types of benefit information and four listed side effects associated with the	<i>Exp. 1 (student sample):</i> Informing people that the medicine had been shown to be effective and would relieve their symptoms within a relatively short time resulted in higher ratings of satisfaction, effectiveness of the medicine, benefit to health and overall effect on health, as well as lower ratings of risk to health. No effect on intention to take the medicine. <i>Exp. 2 (general sample):</i> The effectiveness statement resulted in higher ratings of satisfaction with and helpfulness of the information, appropriateness of the medicine and benefit to health. It did not increase ratings of perceived effectiveness of the medicine. The rationale statement led to significantly higher ratings on the aforesaid measures and resulted in higher ratings of effectiveness of the medicine. No advantage of providing both types of	All three experiments show positive effects of the inclusion of simple benefit information in an explanation about a prescribed medicine. Taken together, they provide a fairly consistent empirical support for the inclusion of such information in medicine information leaflets.

Author, year, country	Objective of study	Involved (type of) medication	Information included in key information section	Evidence for safety & efficacy / feasibility (incl. success factors, potential negative consequences, cost efficacy)	Authors' conclusions
			medicine.	information (helpfulness, effectiveness of medicine). Neither type of statement had an effect on ratings of risk to health or intention to take the medicine. <i>Exp. 3 (general sample):</i> When people were explicitly informed that the medicine was associated with side effects, provision of either type of benefit information resulted in significantly higher ratings of intention to take the medicine. The rationale information positively influenced ratings on all measures, the effectiveness information positively influenced ratings on all measures apart from risk to health.	
Hamrosi et al., 2012 (15), Australia/UK	To explore consumers' beliefs and preferences for benefit information in medicine leaflets and to examine their understanding and reaction to treatment benefits.	PIL for clopidogrel	Three leaflets were developed: the first included a modified section on 'How it Works'; the second had a new General Benefits Statement in addition to 'How it Works'; the third contained the 'How it Works' section and General Benefits Statement plus a further Numerical Benefits Statement based on the numbers needed to treat.	Many participants commented that the general benefits statement acted as encouragement to take the medicine, Several UK participants voiced concerns about the length and readability of PILs when adding benefit information. Australian participants commented about the wording order and presentation. Many Australian (but no UK) participants stated they felt apprehensive and anxious when reading the textual general benefits statement, an opposite effect of its intention. For many, the provision of NNT statistics was too exact, with many participants uneasy and disturbed by the perceived small benefits the NNT portrayed. Textual general benefit statements were preferred. Only a small number of participants embraced the inclusion of numerical benefit information. There were genuine difficulties in interpreting and understanding the NNT. A lack of context provided no comparison to objectively assess the magnitude of the NNT in relation to other medicines or treatments, leading many to make subjective, and often crude, assumptions of the benefit to assign to the medicine. The common belief of participants was that comprehensive medicine information should be available in order to weigh up both the harms and benefits and support informed choice.	The findings of this study support patients' desire for the inclusion of textual benefit information and, to a much lesser extent, numerical data within written medicine information leaflets. However, exactly how to express this information needs further examination.
BBW about the risk of suicidality in paediatric patients taking antidepressants					
Gibbons et al., 2007 (16), USA/NL	To examine whether the public health warnings in the US and Europe led to decreases in SSRI prescription rates for children and	Antidepressants	Public health warnings (among which BBW) issued by FDA, EMA about increased risk of suicidality in paediatric patients	<u>US:</u> From 2002 - 2003, SSRI prescription rates increased for all age groups. After 2003, prescription rates decreased for all groups <60. The magnitude of the decrease in prescription rates is inversely proportional to age. For the ≥60 group, total and new SSRI prescription rates both continued to increase. In children and adolescents, a 14% increase in the suicide rate from 2003 to 2004 was	The rates of SSRI prescriptions for children and adolescents decreased substantially in both the US and the Netherlands. The trends for both prescription and suicide

Author, year, country	Objective of study	Involved (type of) medication	Information included in key information section	Evidence for safety & efficacy / feasibility (incl. success factors, potential negative consequences, cost efficacy)	Authors' conclusions
	adolescents in the US and the Netherlands and whether these decreases in prescription rates were associated with increases in suicide rates in children and adolescents.		taking antidepressants.	observed. In the age group ≥ 60 , the suicide rate has been steadily decreasing throughout this period. NL: Declines in SSRI prescription rates were comparable to those in the US. While the largest decreases were observed in the population < 20 , small decreases were also seen for patients 20–59 years old from 2004 - 2005. SSRI prescription rates for the population ≥ 60 continued to increase. From 2003 - 2005, before and after the warnings were issued, the SSRI prescription rate declined 22% for patients < 20 , and the suicide rate increased by 49% in this age range overall and increased by 44% in boys < 15 .	rates reversed direction in both countries. An overall inverse relationship between SSRI prescription rate and rate of completed suicide was identified for the period 1998–2005. If the FDA's goal is to ensure that children and adults treated with antidepressants receive adequate follow-up care to better detect and treat emergent suicidal thoughts, the current BBW is not a useful approach.
Kurdyak et al., 2007 (17), Canada	To study the effect of the 5 warnings on new antidepressant prescription trends in Ontario. In particular new antidepressant prescriptions in patients < 20 years old.	Antidepressants	UK warning, FDA BBW, advisory Health Canada, all about increased risk of suicide from SSRIs.	None of the 5 warnings had an effect on new prescriptions for SSRIs as a group in any age category. The June 10, 2003, warning in the UK about the use of paroxetine resulted in a significant 54% decrease in new prescriptions of paroxetine issued to patients $< 20y$. The US warnings in 2004 had no effect on the rate of new prescriptions for paroxetine in the age category $< 20y$. None of the 5 warnings were associated with a change in new prescription rates for paroxetine in the 2 age categories for older patients. The 5 warnings had no effect on new prescription rates for antidepressants other than paroxetine in any age category.	A specific warning issued in the UK influenced the prescribing of paroxetine in Ontarians $< 20y$, whereas subsequent, more generalized warnings issued in the US and Canada did not. We speculate that the UK warning had an effect because it was the first of its kind, alternatives to paroxetine were available to physicians and patients, and the warning message was very specific.
Cheung et al., 2008 (18), Canada	To examine the impact of the FDA BBW on the practice of paediatricians in the management of children and adolescents with antidepressants.	Antidepressants	BBW about the use of antidepressants in the paediatric population. The warning also included a number of recommendations around the frequency of follow-up in youth	Responses were received from 670 paediatricians. 484 (72%) respondents were aware of the FDA warning. Of the 484 respondents, 386 (80%) changed their prescribing practices, 154 (32%) followed their patients more closely, while 119 (25%) made a new referral of their patient to psychiatry. 35 respondents (7%) stopped treatment with SSRIs in at least one patient. A further 38 (8%) respondents reported that at least one of their patients stopped the medications because the patient was concerned	The fact that a significant proportion of paediatricians are not aware of the warning should be of concern. Two-thirds of the respondents who were aware of the warning did not increase the frequency of follow-up.

Author, year, country	Objective of study	Involved (type of) medication	Information included in key information section	Evidence for safety & efficacy / feasibility (incl. success factors, potential negative consequences, cost efficacy)	Authors' conclusions
			who are prescribed antidepressants.	about the warning. With regard to specific side effects, 102 (21%) observed agitation and/or aggressive behaviours in patients treated with SSRI's, while 40 (8%) observed worsening depression/suicidality and/or new onset suicidality in these patients.	This emphasizes the need for greater understanding of how warnings are communicated to practicing professionals, and how to increase compliance with FDA recommendations that are in place to ensure greater patient safety.
Olfson et al., 2008 (19), USA	To characterize associations between FDA warning and BBW warnings and antidepressant use.	Antidepressants	BBW: all antidepressants pose significant risks of suicidality in children and adolescents, children and adults treated with antidepressants should be watched closely for increased suicidal thinking or behaviour.	During the BBW study period: <u>Youth</u> : a non-significant decline in the rate of use of each antidepressant. For SSRIs other than paroxetine, this trend represented a significant difference. A non-significant decrease in new use of all antidepressants. <u>18-64 y</u> : paroxetine and tricyclic antidepressant use significantly decreased and use of "other antidepressants" significantly increased. A significant decline in new use of tricyclic antidepressants, but not other groups. <u>>64 y</u> : use of all antidepressants by older adults significantly increased. The rate of new use of all antidepressants by older adults did not significantly change, however, new use of paroxetine significantly declined. New use of tricyclic antidepressants by older adults also significantly decreased. Little evidence that response to BBW varied with patient sex.	The BBW was applied to all antidepressants in children and adolescents. Nevertheless, the effects of BBW on youth antidepressant treatment were most evident for SSRIs other than paroxetine. For the SSRIs, the BBW was associated with a significant deceleration in the rate of youth antidepressant use.
Libby et al., 2009 (20), USA	To determine whether unintended declines in depression care (as result of BBW for antidepressants for young adults) persisted for paediatric, young adult and adult patients.	Antidepressants	BBW about the risk of suicidality for paediatric patients taking antidepressants	After BBW the observed national rate of paediatric case-finding fell significantly. Observed diagnosis rates were significantly lower than history predicted based on the pre-advisory trend; depression rates have continued to decline. Even after accounting for changes to the targeted young adult population, the spill-overs to adults have persisted. For all cohorts, the percentage of newly diagnosed cases fell significantly after the advisory, and the observed rate in 2007 was significantly lower than the trend would have predicted. The change was larger for adult populations (-18%) than for paediatric (-11%).	The major trends in unintended effects (decreased case finding in primary care with no compensatory increase in substitute psychosocial or pharmacological treatment) persisted. Effects on depression treatment were substantial and significant for all ages. The intended effect of FDA policy actions was a decrease in SSRI prescriptions that has proved substantial and

Author, year, country	Objective of study	Involved (type of) medication	Information included in key information section	Evidence for safety & efficacy / feasibility (incl. success factors, potential negative consequences, cost efficacy)	Authors' conclusions
					persistent. The unintended effect was the same persistent decline in the adult cohort, who was never a target.
Foulon et al., 2010 (21), Finland	To analyse and describe changes in prevalence and incidence of antidepressant use in Finland following the BBW issued by the FDA.	Antidepressants	BBW for potential increased risk of suicide or suicidal thinking among children and adolescents taking antidepressants for any indication.	Overall annual prevalence and incidence of antidepressant use increased between 1998 and 2005. There was a significant increase in the monthly incidence of SSRI use, fluoxetine use, and sertraline use post October 2003. When considering pre-advisory trends in antidepressant use, only the incidence of fluoxetine use was higher than the predicted post October 2003 incidence. Use of all other SSRIs was significantly lower than predicted.	Contrary to other countries, the overall incidence of antidepressant use among children and adolescents in Finland continued to increase following the BBW.
Busch et al., 2010 (22), USA	To examine changes in treatment patterns after each (of five) warnings for antidepressant use in children to determine whether specific information contained in these warnings was associated with relevant treatment changes.	Antidepressants	<i>First (06/03):</i> "Paxil should not be used in children <18 for treatment of major depressive disorder." <i>Second (10/03):</i> reports "suicidality in clinical trials of antidepressant drugs in paediatric patients with major depressive disorder." <i>Third (03/04):</i> expanded focus to 10 antidepressant drugs. <i>Fourth (09/04):</i> BBW increased risk of suicidality in paediatric patients for all antidepressant drugs. <i>Fifth (10/04):</i> include BBW labelling (applied to 36 drugs).	Significant declines in use of antidepressant drugs after the fourth warning. After the first warning, paroxetine use declined dramatically from 20 to 8%. Use of fluoxetine increased after the second warning, which first noted the benefits of fluoxetine, from 13 to 16%, although this change was not statistically significant. The use of fluoxetine continued to increase, with a statistically significant increase to 21% of episodes treated with fluoxetine in the following period, and 28% of children being treated with fluoxetine by the last period studied. No significant change in the use of monitoring, conditional on filling a prescription for an antidepressant.	A substantial decline in the use of paroxetine was found and an increase in the use of fluoxetine at time periods consistent with the release of information by the FDA on dangers of paroxetine (first warning) and benefits of fluoxetine (second warning). Release of specific risk and benefit information by the FDA was associated with changes in prescribing, but not outpatient follow-up.
Chen et al., 2011 (23), USA	To examine trends in prescribing antidepressants in ambulatory settings for pediatric patients	Antidepressants	BBW about an increased risk of suicidality among children and adolescents treated	After the FDA advisory, there appeared to be a downward trend in the proportion of depression visits among all visits made by children. The number of depression visits among adults increased without interruption. A seemingly upward trend in the proportion of antidepressant visits among all	This study showed a downward trend in the number of ambulatory visits with a diagnosis of depression, with an

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	before and after the FDA advisory. For comparison, we also assessed these trends in the adult population.		with antidepressant drugs.	visits made by children during the pre-advisory period appeared to be interrupted and reversed after the advisory. Among adults, both the number of antidepressant visits and the proportion of antidepressant visits among all visits increased steadily from 1998–1999 to 2006–2007. Among children, the proportion of visits with an antidepressant prescribed among all depression visits trended upward in the pre-advisory period (54% in 1998–1999 to 66% in 2002–2003) but remained stable after the advisory (65% in 2004–2005 and 64% in 2006–2007). Among adults, neither the number of depression visits with an antidepressant prescribed nor their proportion of all depression visits appeared to be affected by the FDA advisory.	antidepressant prescribed, and with both among children after an FDA advisory on suicidality risk associated with antidepressants. However, children who were diagnosed as having major depressive disorder during an ambulatory visit were no less likely to be prescribed an antidepressant after the advisory than they had been before it was issued.
BBW about the risk of suicidal thinking in paediatric patients taking atomoxetine (ADHD medication)					
Du et al., 2012 (24), USA	To evaluate whether the BBW for suicidal thinking for atomoxetine was associated with a change in the pattern of attention-deficit/hyperactivity disorder (ADHD) medication use.	Atomoxetine	"Suicidal Thinking in Children and Adolescents Being Treated with Strattera (Atomoxetine)". Health care providers and caregivers are advised that children and adolescents being treated with atomoxetine should be closely monitored for clinical worsening, or signs of unusual changes in behaviour, especially during the initial few months of therapy.	The rate of incident atomoxetine use decreased from 29% in 2004 to about 8% in 2007 among incident ADHD medication users. There is no significant change detected in the atomoxetine use rate among targeted children or adolescents after the BBW. There is a significant association between the BBW and the incident use rate in adult patients. The use rate in the adult population decreased by 12% from Sep 2005 to Nov 2005. The trend of atomoxetine use rate was not significant for the post-BBW period, which suggests there was no detectable impact in the long run and the BBW impact was a 1-time shock effect. The long-term measures indicated that atomoxetine incident use dropped significantly before the BBW in all age groups.	A significant decline of the atomoxetine use rate before the BBW was found in all age groups. No significant change in the atomoxetine use rate among targeted children or adolescents after the BBW was detected. The long-term effects of the warning cannot be determined from the data used in this study.
BBW about the increased mortality for elderly patients with dementia taking antipsychotic medications					
Dorsey et al., 2010 (25), USA	To determine impact of BBW on the clinical use of antipsychotics among nationally representative	(Atypical) antipsychotics	BBW that treatment of behavioural disorders in elderly patients with dementia with	Atypical antipsychotic use among elderly patients with dementia decreased by approx. 12,000 mentions from 1 month before to 1 month after the BBW, amounting to a decline of 18%. Among those 65 years or older with dementia, the number of drug mentions decreased from 56	The BBW was associated with a significant decrease in the use of atypical antipsychotics among elderly patients with

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	sample of physicians in the US. Examine whether the BBW was associated with changes in typical drug therapies.		atypical antipsychotic medications is associated with increased mortality.	000 (May 2005) to 28,000 (Dec 2008), an annual decline of 18.5%.	dementia that occurred soon after the BBW was issued. Despite the decrease, atypical antipsychotics still comprised 9% of prescription drug uses for dementia among elderly patients at the end of 2008.
Lester et al., 2011 (26), USA	To assess changes in antipsychotic use patterns as result of the BBW as well as alternative measures that have been used for behavioural symptom management.	Antipsychotics	BBW that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death	Nearly 60% of directors of NHs reported that at least 20% of their residents are taking antipsychotic agents. Nearly 80% of the directors reported that the number of residents receiving antipsychotics since the BBW has either decreased (39.1%) or remained unchanged (39.1%). Only a small number (2.9%) reported an increase in antipsychotic use. The most commonly reported change in care was using lower doses of antipsychotics (64.7%). Use of non-antipsychotic medications was reported in 59.7% of facilities. In 53.2% of facilities obtaining more frequent psychiatry / psychology consults before prescribing antipsychotics was reported. Increased use of non-pharmacologic interventions in 52.7% of facilities.	Our study reveals that antipsychotic medications are still widely used in the NH setting in spite of the BBW, with most directors reporting that over 20% of their residents are prescribed antipsychotics. Notably, only 39.1% of facilities report reduced usage of antipsychotics since the BBW.
BBW about the serious cardiac arrhythmias for patients taking droperidol					
Habib et al., 2008 (27), USA	To determine the practice of members of the Society of Ambulatory Anesthesia (SAMBA) in the management of postoperative nausea and vomiting (PONV) before and after the FDA BBW on droperidol.	Droperidol	BBW on droperidol because of concerns of serious cardiac arrhythmias secondary to QT prolongation.	74% of 292 respondents indicated that droperidol was available in the formulary in their hospital, 15% reported it was not available. 11% reported that droperidol was available before the BBW but not afterward. 74% of 230 respondents replied that no restrictions were made as to its availability or use, 10% indicated that the hospital has changed the location where droperidol is stocked, and 22% reported that the hospital placed restrictions on its use. The choice of other antiemetics not involving droperidol was significantly higher after the BBW. The choice of droperidol as a first-line agent for the treatment of established PONV was also significantly less after the warning.	The choice of droperidol as a first-line agent for the management of PONV has significantly declined after the BBW, despite that 92% of respondents did not believe that the BBW was justified.
Compliance with BBW regarding drug-drug, drug-laboratory and drug-disease warnings					
Lasser et al., 2006 (28), USA	To determine how frequently physicians and other providers prescribe drugs in	Medication for outpatients that contained a BBW pertaining to drug-	BBW for drug-drug, drug-laboratory and drug-disease warnings	33 778 (10.4%) patients received medication that contained a BBW pertaining to drug-drug, drug-laboratory, and/or drug-disease interaction. Of these patients, 2354 (7.0%, or 0.7% of all outpatients) received a prescription in	Although a few outpatients seem to receive prescriptions in violation of BBW for drug-drug, drug-

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	violation of BBWs pertaining to drug-drug, drug-laboratory, and drug-disease interactions.	drug, drug-laboratory and/or drug-disease interaction.		violation of the BBW. Most patients who received a prescription with BBW were at risk for drug-disease interaction (90.6%), followed by drug-laboratory interaction (26.6%) and drug-drug interaction (3.3%). In 367 BBW violations, 4 ADEs related to the BBW violation (1.1%), 4 ADEs unrelated (1.1%), 92 potential ADEs (25.1%), 154 medication errors (42.0%). Among 4 ADEs related to BBW violation, 3 were rated as serious and 1 as significant; all were deemed preventable.	laboratory, and/or drug-disease interactions, the absolute number of outpatients at risk is substantial. To increase adherence to BBWs, these need to be clarified, simplified, and made consistent with commonly used practice guidelines.
Wagner et al., 2006 (29), USA	To assess frequency of use of BBW medications in ambulatory care and prescribing compliance with BBW recommendations	216 BBW medications / groups	Description of risks and (optionally) specific precautions for the drug's use.	42% received at least one dispensing of BBW medication that could apply to them. Almost half of 74,666 new dispensings of BBW medications with baseline monitoring recommendations had no claim for the test. No claims for recommended laboratory test for 13% of episodes of continued use of BBW medications that should be accompanied by routine monitoring. 9% of dispensings of the 4 drugs with warnings about co-medications were prescribed on the same day as a contra-indicated drug. Women of childbearing age received 78,840 dispensings of BBW medications that should be avoided during pregnancy.	More than 40% of ambulatory care patients received at least one potentially relevant BBW medication during a 30-month study period, and compliance with BBWs was highly variable.
Ricci et al., 2009 (30), USA	To improve the understanding of prescribing and patient-monitoring practices of physicians prescribing BBW medications to patients >65 years in the ambulatory care setting.	carbamazepine, amiodarone, ketoconazole, loop diuretics, methotrexate, cyclosporine, metformin and combinations, and cilostazol	BBW for eight medications, six of which were drug-laboratory warnings and two were drug-disease warnings.	Patients prescribed drugs with a drug-laboratory warning had lower rates of prescriber BBW compliance (0.7%-24.9%) than patients prescribed drugs with a drug-disease warning (84.7%-90.2%).	Administrative claims analysis identified low rates of prescriber compliance with BBWs in managing patients age >65 years.
Broader perspective on BBWs					
Matlock, 2011 (31), USA	To describe the history of BBW, its original intent and highlight inconsistencies in application of the warnings and their reception by the	Examples were droperidol and methadone.	N/A	Despite the rarity of serious events, clinical use of droperidol for post-operative nausea and vomiting has decreased sharply, and sales of droperidol dropped 10-fold in the year after its boxed warning was issued. In contrast to droperidol, the number of new methadone prescriptions has not decreased in the years following its boxed warning, despite risk of the same cardiac arrhythmia and risk of respiratory depression.	With renewed focus, clarity, and modest modifications, the FDA BBW may increasingly reflect the best evidence available relative to clinical practice, improve the use of medications by

Author, year, country	Objective of study	Involved (type of) medication	Information included in key information section	Evidence for safety & efficacy / feasibility (incl. success factors, potential negative consequences, cost efficacy)	Authors' conclusions
	<p>medical community. To highlight some unexpected consequences and provide suggestions for improving its usefulness to clinicians.</p>				<p>healthcare providers, and enhance patient care and safety. Seven recommendations to potentially improve the application of the BBW are given.</p>

3.2.2. Grey literature

The search for grey literature concerning the inclusion of a key information section in the PIL and SmPC yielded few additional documents. The relevant results from these documents are presented in this paragraph.

A. Introducing a headline section in the PIL in the UK

The UK Medicines and Healthcare products Regulatory Agency (MHRA) 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. In their report "Always Read the Leaflet, getting the best information with every medicine" (2005), this group suggested three improvements for better risk communication (1):

- 1) Provide access to the most important information for safe and effective use by the use of headlines.

The length and complexity of the PIL appears to discourage patients to read the whole PIL. Providing a short summary of key information, a 'headline section' at the very beginning of the PIL, could be useful.

- 2) Balanced information on the risks of the medicine with information on its benefits.

Much of the information given in the PIL relates to possible side effects, which might frighten patients and discourage them to take the medication. Not only optimising the information on side effects is important (see the next point), but including information about the benefits of the medication can support patients in their judgment about the medication.

- 3) Provide better information about side effects.

A good understanding of the information about side effects by patients is crucial. The Working Group provided a number of key principles on how to express the magnitude of the risk.

In their report, the Working Group published a guideline on how to provide information about risks and benefits in the PIL. This guideline is presented in Appendix 2 It is divided into three sections (following the three improvements for better risk communication described above): a) presenting headline information, including an example of a headline section, b) presenting benefit information and c) presenting information on side effects. This guideline proposed by the MHRA might be useful for deciding on which information to be included in the key information section and how to present this information, as well as design aspects. However, it is important to recognize the need for user testing in order to identify possible factors that negatively influence the comprehensibility of the presented information. The example of a headline section to be included in the PIL for the anticonvulsant carbamazepine, proposed in the report by the MHRA, was user tested in the study of Dolk et al. (2011)(9) - see paragraph 3.1.1.

Impact of a headline section in the PIL

In addition to the study by Dolk et al. (2011) identified in the electronic database search, the grey literature search identified an abstract orally presented at the Health Services Research & Pharmacy Practice Conference by Dickinson and colleagues, in which the impact of such a section on patient satisfaction, knowledge and behavior was explored with focus groups (33). This study revealed that inclusion of a headline section was valued by participants, and they indicated that including information on what the medicine is for, dosage, contraindications, drug-interactions and side-effects

would be appreciated. The headline section would also be more likely to be read by those who do not regularly read the leaflet, although including such a section might also lead to people not reading the whole PIL.

B. The proposed 'Medicine Information Box' for OTC-medication in Australia

In 2012, the Therapeutic Goods Administration (TGA) – a division of the Australian Government Department of Health and Ageing – published the consultation paper "Medicine Labelling and Packaging Review" (34). This paper primarily aimed at how information should be presented on the medicine containers or boxes within which they are supplied. One of the issues recognized as a risk for consumer safety is the lack of a standardised format for presenting information. Standardising information supports consumers in comparing different products with the same active ingredient and as such helping them to make a well-informed choice between these products. In addition, no consistent location for this information was required. Consistent placement supports consumers to easily locate important information. In this paper, recommendations are presented for a standardized format for the 'Medicine Information Box' (Figure 1).

This Medicine Information Box is proposed to be used to present the required information on labels of over-the-counter (OTC) medication in Australia. It contains the mandatory headings 'active ingredient', 'uses', 'warnings and allergy information', 'directions', and 'storage information'. This box is based on the 'Drug Facts Box' used for OTC medication in the US. The TGA's recommendations are presented in Box 3.5.

Medicine Information Box
Active ingredient
Glucosamine sulfate sodium chloride complex 1886 mg (equivalent to glucosamine sulfate 1500 mg) Chondroitin sulfate-bovine soidum 95% 842 mg (chondroitin sulfate sodium 800 mg)
Uses
<ul style="list-style-type: none"> • May help to relieve osteoarthritis joint pain • Helps reduce cartilage wear • Chondroitin provides nutrition to the joints
Warnings and allergy information
<ul style="list-style-type: none"> • Glucosamine is derived from seafood. Not recommended for people with seafood allergies • Contains approximately 228 mg sodium per daily dose • May occasionally cause mild gastrointestinal symptoms • Check with your doctor or pharmacist if you are taking any other medications
When using this product
If pregnant or breastfeeding, ask a health professional before use Keep out of reach of children. In case of overdose, seek medical attention or call the poisons information line on 13 11 26
Directions
Adults - Take 1 easy to swallow tablet twice daily with meals or as professionally prescribed Children under 12 years - Only as professionally prescribed. If symptoms persist, see your healthcare professional
Storage information
White, vanilla flavoured tablet with easy to swallow coating. Store below 30C. Protect from moisture

Figure 1. Medicine Information Box, taken from TGA (2012)

Box 3.5: Recommendations for a standardized information format (taken from the paper “Medicine Labelling and Packaging Review” (34)):

1. Mandated information on labels and packaging of non-prescription medicines and complementary medicines is presented in a standardised Medicine Information Box, based on the US FDA Drug Facts box. The mandatory headings are:
 - Active ingredient, including the amount in each dosage unit
 - Uses (indications)
 - Warnings and Allergy Information (including when the product should not be used and when to consult with a doctor or pharmacist. This section also includes information about possible side effects and substances or activities to avoid. The final lines of this section should include information about preservatives in the product.)
 - Directions/Dosage instructions
 - Storage information.
2. The font height for information must be no smaller than 1.5mm, with heading height at least 2mm.
3. The Medicine Information Box must have a white background with black text. Headings must be highlighted or bolded so they are sufficiently emphasised.
4. Where there is insufficient room on a single face of a package, the box may be split over more than one face. However, the overall format of the information is to remain the same. In these instances a pack insert may also be included containing the Medicine Information Box as a continuous table.
5. Information about the presence in the medicine of an allergen listed in Schedule 1 of TGO 69, which may be amended, must be included under the heading Warnings and Allergy Information.
6. For products containing more than 3 active ingredients, or products in small containers, there may be insufficient space on the medicine container or primary packaging for a complete Medicine Information Box. In these cases a complete Medicine Information Box should be included as a pack insert. The minimum information to be included on the label will include information under the following headings:
 - Directions
 - Warnings and Allergy Information.

Where space restrictions do not allow for the required information to be provided in the Medicine Information Box, an alternative arrangement or formatting of information should be provided to the TGA for assessment and approval, together with a justification for non-standardised presentation. This may include breaking the information over more than one panel, or reduction in font size.

Although this standardized format for a Medicine Information Box is developed to be included on labels of OTC medication, the included information and/or its presentation might serve as an example for the key information section for the PIL.

C. The 'Drug Facts Label' for OTC-medication in the US

In 2002, the FDA required over-the-counter drug manufacturers to use the new, standardized 'Drug Facts Label' (Figure 2). Simple language and a clear structure needed to be used to support patients in comparing and selecting OTC-medications and to follow instructions on how to use the medication. In addition, the type size needed to be large enough to be easily read and specific layout details (e.g. bullets, line-spacing and clearly marked sections) were required for better readability (35). The FDA obliged manufacturers to include information in a certain order (Box 3.6).

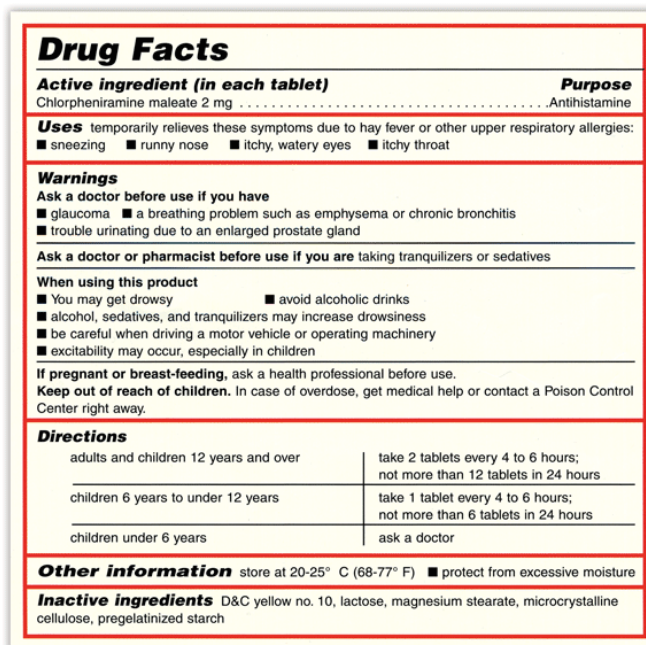


Figure 2. Drug Facts Box, taken from FDA (2002)

Box 3.6: Mandatory information for the Drug Facts Label (taken from "New OTC Drug Facts Label", FDA 2002 (35)).

The following information must appear in this order:

- The product's active ingredients, including the amount in each dosage unit.
- The purpose of the medication.
- The uses (indications) for the drug.
- Specific warnings, including when the product should not be used under any circumstances, and when it is appropriate to consult with a doctor or pharmacist.
- The warnings section also describes side effects that could occur and substances or activities to avoid.
- Dosage instructions addressing when, how, and how often to take the medication.
- The product's inactive ingredients, which is important information for those with specific allergies.

Similar to the Medicine Information Box used in Australia, this Drug Facts Box might be useful as an example for the key information section in the PIL.

D. Benefit and harm information in direct-to-consumer advertisements

Two studies, both from Schwartz et al., were identified in which the inclusion of a 'Drug Facts Box' in direct-to-consumer advertisements (DTCA) was evaluated (36;37). Although it carries the same name, this box is different from the Drug Facts Box required by the FDA and previously described (see C). The Drug Facts Box developed by Schwartz and colleagues is a one page summary that includes descriptive and quantitative information of the advertised drug. An example of their Drug Facts Box for the drug tamoxifen is presented in Figure 3. Information on the benefits and side effects of the drug, based on data from published trials from the FDA's drug approval process, is presented in the table.

Drug Facts: TAMOXIFEN (No Ivdex)		
What is this drug for?	To reduce the chance of getting breast cancer	
Who might consider taking it?	Women at high risk of getting breast cancer (1.7% or higher risk over 5 years). You can calculate your breast cancer risk at http://bcra.nci.nih.gov/btc .	
Who should not take it?	Women who are pregnant or breastfeeding	
Recommended testing	Have a yearly checkup that includes a gynecological examination and blood tests	
Other things to consider doing	No other medicines are approved to reduce breast cancer risk for women who have not had breast cancer	

TAMOXIFEN STUDY FINDINGS TABLE		
13,000 women at high risk of getting breast cancer were given TAMOXIFEN or a sugar pill for 6 years. Here's what happened:		
What difference did TAMOXIFEN make?	Women given a sugar pill	Women given TAMOXIFEN (20 mg a day)
Did TAMOXIFEN help?		
Fewer women got invasive breast cancer	2.7%	1.4%
Fewer women died of from breast cancer	0.09%	0.05%
Did TAMOXIFEN have side effects?		
<i>Life-threatening side effects</i>		
More women had a blood clot in their leg or lungs	0.4%	0.8%
More women had a stroke	0.4%	0.6%
More women got invasive uterine cancer	0.2%	0.5%
<i>Symptom side effects</i>		
More women had hot flashes	69%	81%
More women had vaginal discharge	35%	55%
More women had cataracts needing surgery	1.1%	1.7%
Other things to know		
Dying for any reason	1.1%	0.9%

How long has the drug been in use?
Tamoxifen was first approved by the FDA in 1982 - Studies show that most serious side effects or recalls of new drugs happen during their first 5 years of approval.

Figure 3. Tamoxifen drug facts box, taken from Schwartz et al. (2007)

Although this box is used in DTCA, which is not within the scope of this project, it may provide useful information for a key information section in which benefit and harm

information must be balanced. Therefore, these two studies are included and discussed in this paragraph.

In the 2007 study, the tamoxifen Drug Facts Box is tested for its readability and understandability. Most of the participants were college educated (38%) and/or had a post-graduate degree (31%). It was found that most participants were able to find specific data in the box, to understand the information and to use the data (apply the information) to decide for example whether the drug was suitable for various patients (36). The authors suggest that their presentation of the benefits and harms of a drug can be useful in a broader perspective than just DTCA.

In the 2009 study, two randomized controlled trials tested whether the inclusion of a Drug Facts Box (the format that was used in the previous study, see Figure 3) in direct-to-consumer ads improved consumers' knowledge about the drug and whether the box supported them in making a choice between two alternative treatments. In one trial, two ads for drugs to treat heartburn (histamine-2-blocker and a proton pump inhibitor) were tested; in the other trial two ads for drugs to prevent cardiovascular events (statin and clopidogrel) were tested. In the two studies, 41% and 32% of participants respectively were college educated or higher. It was found that consumers who were provided with ads including the Drug Facts Box had a more accurate perception of the benefits and harms of the specific drug than consumers who were provided with the ads without this box (37).

3.3 Summary

The literature study described in this chapter shows that examples of key information sections are available, but literature includes limited evidence on the added value. In the UK (headline section), Australia (medicine information box) and the US (Drug Facts box and Black Box Warnings), a type of key information section is already in use or proposed, albeit on the package label in Australia and the US, rather than in the PIL. The Drug Facts box developed for inclusion in direct-to-consumer advertisement also presents a format for balanced benefit/harm medication information.

Yet, while the number of examples of key information sections seems to be growing, the evidence on the added value of a key information section is limited, especially when it concerns key information sections combining risk and benefit information. The only study on adding a key information section also including benefit information to the PIL concluded that *the headline section did not influence 'findability' or comprehension of information in the PIL*. Furthermore, the PIL with the headline section was perceived to be as difficult, well designed and useful as a PIL without this section. Yet, participants were enthusiastic about the section and thought it was an improvement to the PIL. Moreover, including benefit information in patient information shows that this information increases patients' knowledge about the medicine and their judgment (e.g. effectiveness of the medicine, its benefit to health and their satisfaction with the provided information) of the medicine. The only country in the European Union where key information sections (headline sections) are used is the United Kingdom (UK). Currently, only two studies testing these UK headline sections have been performed, one on the PIL and one on the SmPC.

Overall, it can be concluded that there is little evidence available yet for the added value of including a key information section with balanced information on the benefits and the risks of the medication in the PIL and/or SmPC, nor for its feasibility and cost-effectiveness. Experiences and guidelines from the UK may be helpful for further developments at the EU level.

4 Results stakeholder survey

The next phase of the study was a stakeholder consultation through both an online survey and an online discussion. This chapter contains the methods and results of this consultation. It should be noted that we stressed to all stakeholders that there is no decision made yet about whether or not to include adding a key information section to the PIL and the SmPC at the European level.

4.1 Methods

A structured questionnaire was developed in order to capture stakeholders views on the key information section. These questionnaires were sent out to different stakeholders. Afterwards an online discussion was held with a smaller number of participants.

4.1.1 Participants online survey

European and national representatives of the following organizations were approached:

- Patient and consumers;
- Physicians and pharmacists (health care providers=HCP);
- Pharmaceutical industry;
- Regulatory Officers;
- Communication experts

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 member was searched for contacts. All representatives were contacted by email and were given the opportunity to fill in the on-line questionnaire. Two reminders were sent to participants by email to those 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 (SvdB). Table 4.1 shows the response for every stakeholders group. It proves that – despite our efforts to increase the response – the response was low among all stakeholders except the communication experts and (to a lesser extent) the pharmaceutical industry.¹¹

¹¹ A substantial number of pharmaceutical industry representatives did not provide the name of their organizations. Therefore, no list is included for them.

Table 4.1: Response among the representatives of different stakeholders' representatives

Questionnaires	Patient and consumers organizations	Health care providers organizations	Pharmaceutical Industry	Regulatory offices	Communication experts
Number sent out	492	192	59 + forward to other organizations	64	10
Net response	42	12	40	16	8

4.1.2. Online questionnaire for survey

All representatives received a link to an online questionnaire by email. This questionnaire could be accessed as many times as participants wanted, until they had completed the questionnaire and submitted it. The questionnaire was written in English and aimed at providing answers on the following aspects:

- Opinion on adding a key information section to the PIL and/or SmPC for improving safety and efficacy of medicines' use;
- Type of information considered to be relevant to be added to such section;
- Challenges in relation to the drafting of a potential key information section in PIL and in SmPC when it comes to a balance of information to be scientifically valid and, at the same time, provide additional value in terms of faster and easier identification of the necessary key information (including cost efficacy of the inclusion of key information section);
- Challenges in relation to the drafting of a potential key information section when it comes to the lay-out and design of the PIL and SmPC;
- Assessment of potential positive and negative effects of a key information section;
- Advantages and disadvantages of possible alternatives for a key information section (such as highlighting existing sections);
- Foreseen changes of adding a key information section in terms of EU legislation;
- Added value of a key information section for users, i.e. patients (including vulnerable patients, for example low literate patients) and health professionals.

Every group of stakeholders received the same questionnaire, except for patient organizations not having to answer the questions about SmPCs (Appendix 3).

4.1.3 Method online discussion

Online discussions have been introduced as an alternative method (compared to traditional focus group discussions) in qualitative research. Participating in online discussions is convenient and comfortable since participants are unconstrained by place and time and can choose to participate at a moment that is convenient to them. We chose the so-called asynchronous mode of the mediated online discussion method (Tates 2009). This means that experts were 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 follow-up

questions if needed. The main goals of the online mediated discussion was to derive recommendations for improvement of PIL and SmPC for a related project on the comprehensibility and readability of the PIL and SmPC (the PIL-S project; Van Dijk et al 2013). There were five topics organized around the shortcomings of PIL and SmPC. 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 forum. The last day of the first week, the results from the first four days were summarized 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. As we noticed from the survey that problems with the SmPC were much less frequently reported and experienced, we decided to focus on the PIL in the online discussions. In total 20 participants were involved in the online discussion: two representatives of European level patient organizations, three representatives of health care professional organizations, 4 regulatory officers, 7 experts on communication in the PIL and 5 representatives of the pharmaceutical industry. It should be noted that the pharmaceutical industry had a separate forum for discussion because they may have different interests from other groups in relation to a key information section.

4.2 Participants of the online survey and their characteristics

European and national representatives of patient and consumer organizations, health care providers (physicians and pharmacists), pharmaceutical industry, regulatory offices and communication experts were approached. We made an effort to include representatives of European level organizations and their national members. Table 4.2 shows the characteristics of all participants. The table shows that for some characteristics a considerable part of the participants chose the option 'other'. To get a complete image of the participants the category 'other' will be described per group of stakeholders when necessary.

The professional background of the respondents widely varies, but overall a pharmaceutical background is often mentioned among representatives of HCPs (50%), pharmaceutical industry (68%) and regulatory offices (81%). Almost half of the representatives of patient and consumer organizations (45%) state that they have another professional background (than legal/medical/pharmaceutical/social). These include for example: clerical administration, economics, health science, international business, linguist and management, or medical journalist. Professional backgrounds that are named by communication experts are: graphic design, nursing, linguistics and document design, visual communication and writing, editing, consumer research. Current positions varied both between and within the different groups of stakeholders. Patient and consumer organizations representatives mention current positions such as: board member, development officer, honorary president, journalist, trustee and administrator, chairwoman, founding member, and researcher. Other positions of health care providers include for example clinical academic fellow, communications officer, international affairs officer, member of presidium, board member, and clinical guidelines manager. The pharmaceutical industry also has respondents working elsewhere than named in the questionnaire such as regulatory affairs manager or officer and pharmacy technician. Regulatory officers also do have some different current positions such as, head of unit, preclinical and clinical assessor, quality assessor, or scientific assessor.

Participants are from a wide variety of countries in the EU, with an overrepresentation for the UK, the Netherlands, Sweden and Belgium. This is probably due to the fact that

questionnaires were provided in English. Most participants worked in national organizations. The proportion of participants working in European level organizations was 17% for HCPs, 19% for patient organizations and 27% for the pharmaceutical industry.

When asked for their involvement with the PIL in their daily work, most of the respondents state that they are involved with the PIL (sometimes to always). Representatives of HCPs and patient and consumer organizations are least frequently involved with the PIL during their daily work. The same picture arises for involvement with the SmPC (patient organizations not asked).

Table 4.2: Participants characteristics in percentages per group

	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		
Slovenia				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

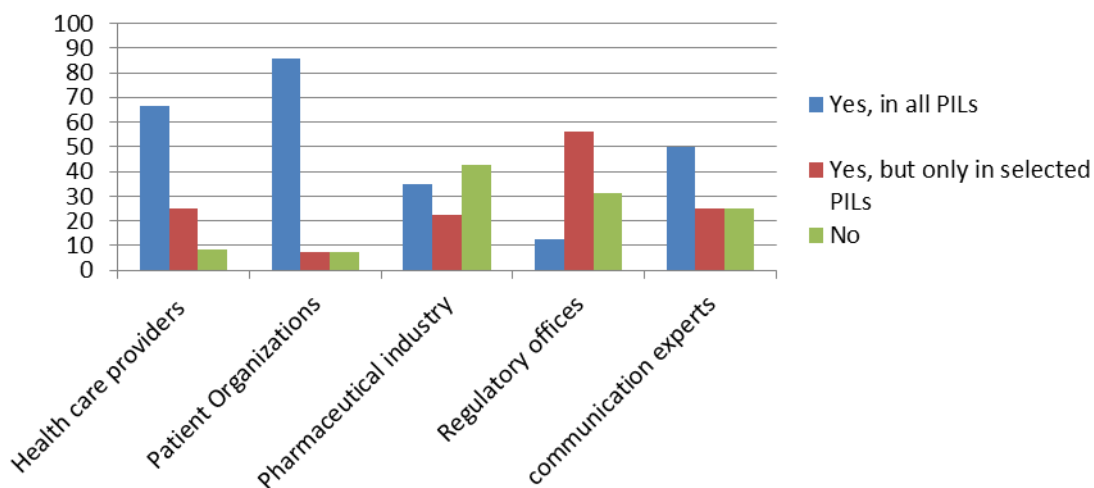
4.3 Results online survey

This section provides the results of the stakeholder consultation. Mostly results are presented in figures, to support the readability of the text, all details can be requested from the authors.

4.3.1 Support for addition of a key information section to PIL and SmPC

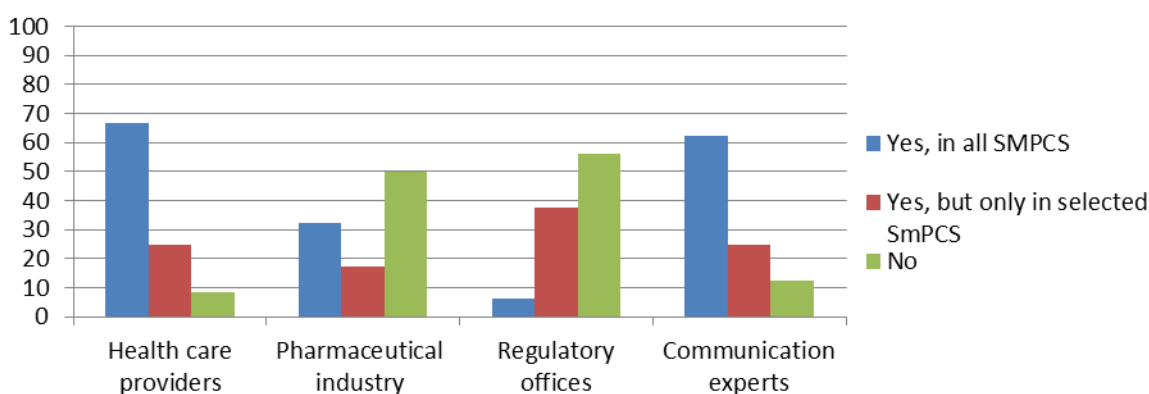
First of all respondents were asked whether or not they are in favour of adding a special section with key information to the PIL and SmPC respectively (Figure 4.1). Most respondents are in favour of a key information section in the PILs, especially the health care providers (67%) and the patient organizations (86%). Regulatory offices most frequently favour a key information section in selected PILs only (56%). The pharmaceutical industry is most divided: just over 30% is in favour of a key information section, whereas just over 40% is against such a section.

Figure 4.1: Percentage of participants in favour of a key information section for PILs.



For the SmPC, the picture is comparable: the majority of HCPs (67%) and communication experts (63%) and a minority of regulatory officers (6%) and pharmaceutical industry representatives (33%) is in favour of adding a key information section to all SmPCs (Figure 4.2).

Figure 4.2: Percentage of participants in favour of a key information section for SmPCs.



A few respondents explained the motivation for their preference briefly in the questionnaire. One communication expert said; "I am broadly in favour of including a summary information box, but I can see that there may be occasions when it is inappropriate or impractical. I think user testing will give a clearer idea as to when and how summary boxes can be most useful". Another communication expert added: *'It is imperative that the key information section is present to highlight the sections that*

are key to be included in consultations between health care professionals and patients'

4.3.2 Lay-out of a key-information section

Respondents were asked about a possible lay-out for a key information section. Looking at the results, it shows that according to half to a majority of the participants (75% of health care providers, 71% of patient organizations, 48% of pharmaceutical industry, 50% of regulatory offices and 63% of communication experts) a key information section should be placed at beginning of the PIL and SmPC or as a cover on the front page (results not presented in figure).

The majority of respondents think the key information should come in a text box in the PIL, rather than a shaded box, with the exception of communication experts (67% of health care providers, 64% of patient organizations, 53% of pharmaceutical industry, 69% of regulatory offices and 25% of communication experts). It should be noted that among the pharmaceutical industry representatives and regulatory officers a considerable proportion stated that they were not in favour of both a shaded or a text box (17.5% and 12.5% respectively) (results not presented in figure). For the SmPC, results are comparable: a majority is in favour of the key information section to be included in a text box rather than a shaded box (67% of health care providers, 50% of pharmaceutical industry, 69% of regulatory offices and 25% of communication experts). Here, 15% of the pharmaceutical industry representatives and 25% of the regulatory officers state they are not in favour of a shaded nor a text box.

Figure 4.3 shows the results about the preference as to how to lay out the text in a key information section for the PILs. The use of bolded text is most frequently mentioned by all stakeholder except regulatory officers and communication experts and second comes usage of a bigger font. Using different colours is the least favourite way of highlighting the key information section. For the SmPCs the results are comparable (Figure 4.4). Again most participants are in favour of bolded text, even more than in case of the PIL.

Figure 4.3: Percentage of participants in favour for type of layout of the text in a key information section in the PILs.

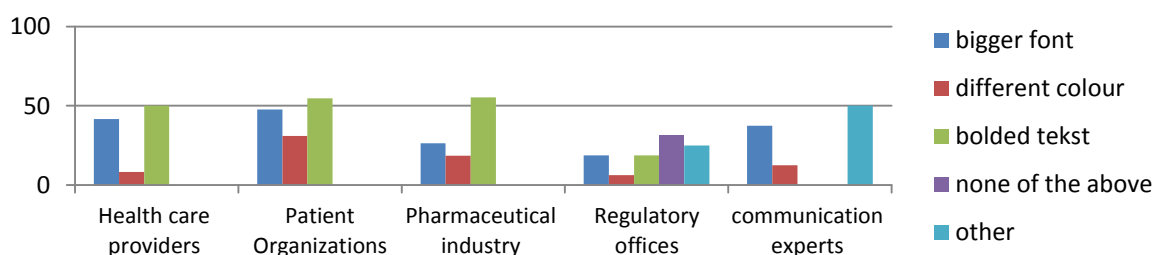
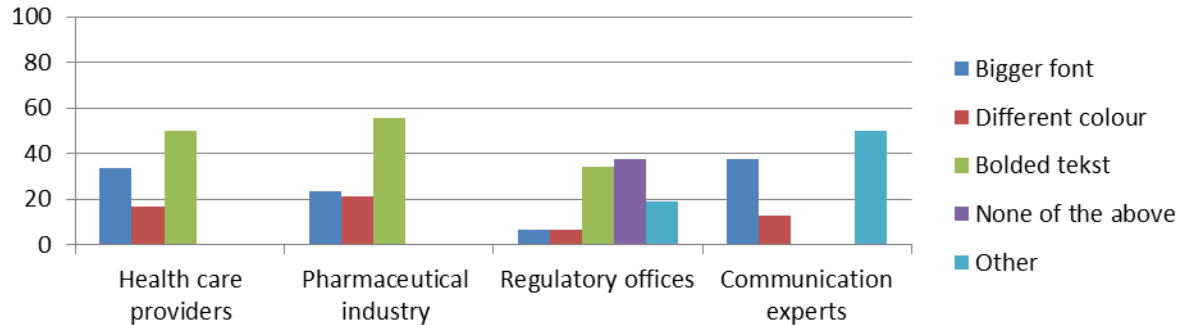


Figure 4.4: percentage of participants in favour for type of layout of the text in a key information section in the SmPCs.



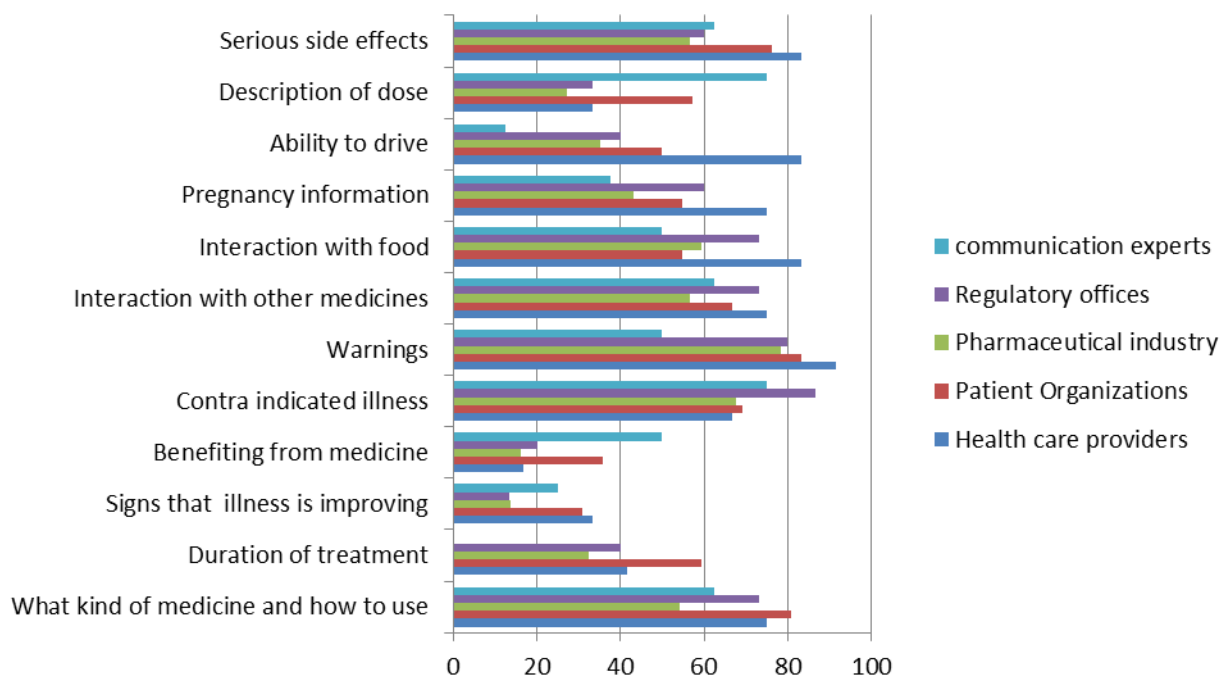
When it comes to organizing the key information section **bullet points** show to be favoured by of the majority of the participants (PILs: 82,2%; SmPCs: 75%) when compared to paragraphed text.

4.3.3 Content of a key-information section

Respondents were also asked to give their opinion about what information would be key to put in a special section of information in the PIL and SmPC. Figures 4.5 and 4.6 show the results.

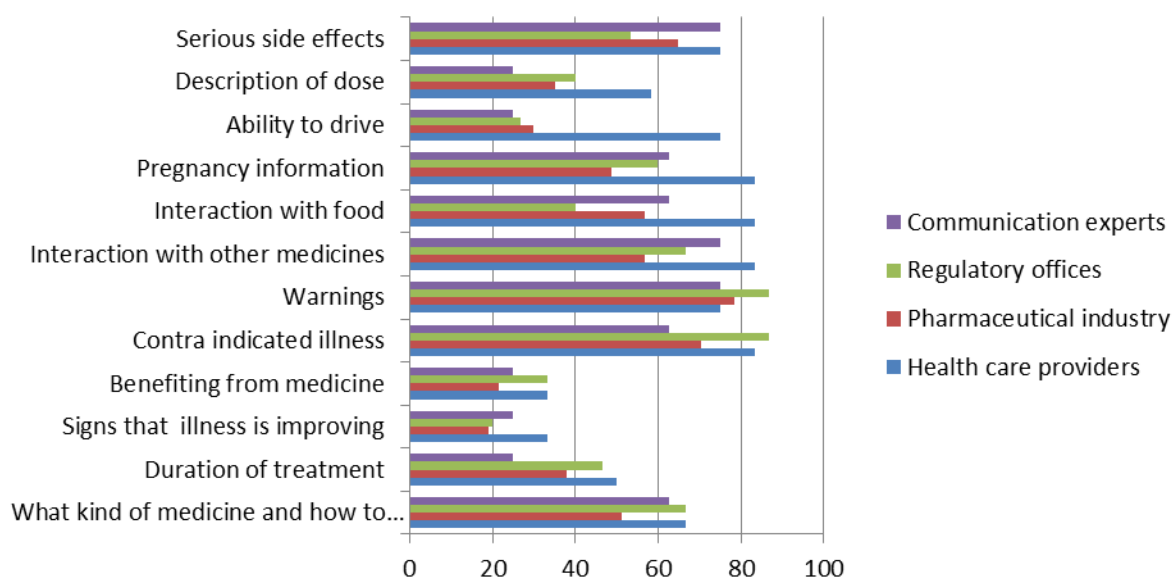
For the PIL a large majority of all stakeholders (except communication experts) consider warnings to be of relevance for the key information section. Other topics that should be included according to a majority of the respondents are contra indicated illness and serious side effects. A majority of the health care providers also stress the need to include information on the practical side of taking medication: according to a majority of them information about taking the medication and pregnancy, ability to drive and interaction with food or other medicines is of relevance for the key information section as well. The majority of patient organization representatives is also in favour of adding information on what kind of medicine the PIL is and how to use the medicine to the key information section, as well as information on interactions with other medicines and with food and information on the duration of the treatment. Pharmaceutical industry representatives generally are less supportive of adding topics to the key information section compared to other stakeholders. Communication experts are more in favour of adding benefit information to the key information section than any other stakeholder. Overall, a minority of stakeholders is in favour of adding such benefit information to a key information section. These results show that patient organizations and HCPs have different opinions as to what key information is which stresses that key information in the SmPC and the PIL are not necessarily the same.

Figure 4.5: Percentage of participants in favour of information to put in a key information section in PILs.



Again, results for the SmPC are comparable to those of the PIL (Figure 4.6): warnings and contra indicated illness are considered to be of great importance to include in a key information section as is information on interaction with other medicines and serious side effects. Health care providers also think that it is important for the SmPC to include information about interaction with food and about pregnancy and ability to drive are taken into account in the key information section. A minority of all stakeholders thinks benefit information should be included in a key information section.

Figure 4.6: Percentage of participants in favour of information to put in a key information section in SmPCs.



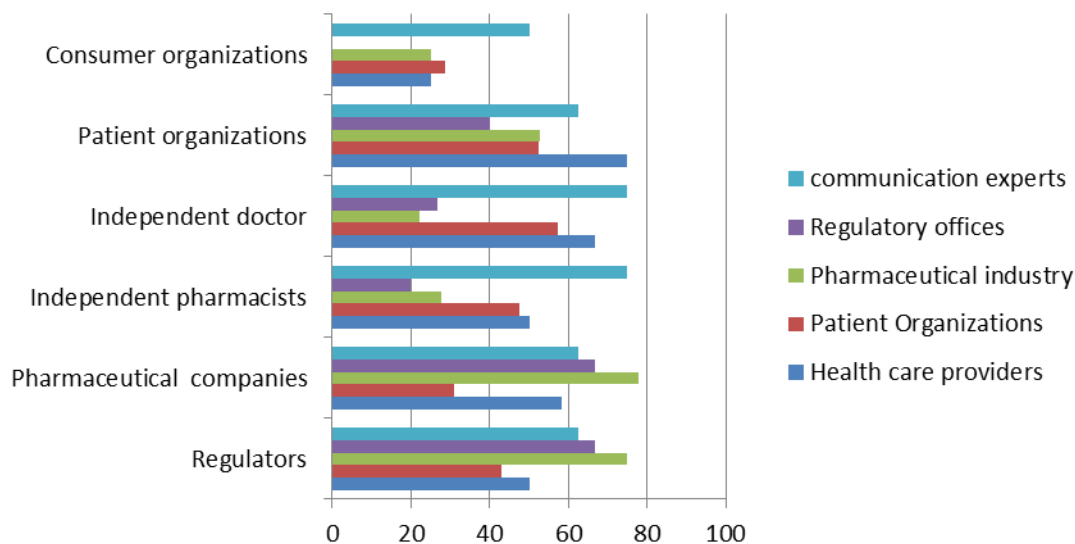
When asked how many issues should be included in a key information section, most participants (PIL: 47% and SmPC: 42%) answered that five to ten points should be included, followed by up to five points of information (PIL: 35%; SmPC: 34%). Representatives of patient organizations and communication experts more often opted for 5-10 issues to be included in the PIL than HCPs, pharmaceutical representatives and regulatory officers who opted more often of a maximum of 5 issues.

In all stakeholder groups the majority of respondents (85% for the PIL and 76% for the SmPCs) think that all or a part of the information presented in a key information section should be referenced to the information in the main text i.e be cross-referenced. There is no clear consensus about whether all information should be cross-referenced or only the information on those issues where the full text of the PIL or SmPC provides more information, albeit overall there is a slight preference for this last option (34 and 47% respectively) in case of the PIL. For the SmPC both options are equally often mentioned (37 and 38 % respectively). Representatives of patient organizations and health care providers are more often in favour of cross-referencing than the other three stakeholders. While 2% of the patient organizations representatives and 8% of the HCPs think cross-referencing is not needed, these percentages are 21%, 33% and 25% for the pharmaceutical industry, regulatory officers and communication experts respectively. The right way to cross-reference needs to be found. A communication expert added as a comment to this question: *"From a practical point of view using a graphical symbol would be the easiest way, but you need to find one that is widely recognized and understood"*.

4.3.4 Who needs to provide input to a key information section

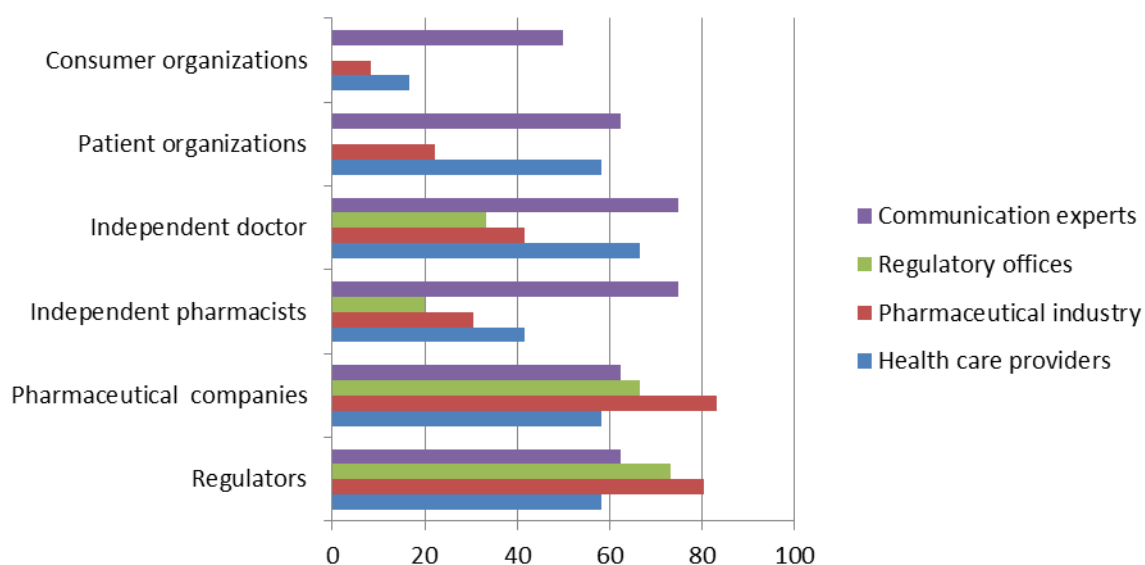
Respondents were asked who should provide input for a key information section in the PIL in order to select the best information (figure 4.7). The results show a mixed opinion. HCPs most frequently mention patient organizations and independent doctors as the ones who should provide input. Pharmaceutical industry and regulatory officers, however, most frequently mention pharmaceutical companies and regulators as the ones that should give their input.

Figure 4.7: percentage of participants in favour of a stakeholder to give input on the points of information for a key information section in the PILs.



The results for the SmPC are presented in Figure 4.8. About two third of the HCPs think that independent doctors should provide input as to which information should be included in the SmPC. Between 40-60% of the HCPs think that input of the other stakeholders is needed, with least support for the input of an independent pharmacist. About 80% of the representatives of the pharmaceutical industry think that the industry and regulators should be involved in providing input. Also regulators think that these two parties should be involved although the percentage agreeing so is slightly lower than among the pharmaceutical industry representatives.

Figure 4.8: percentage of participants in favour of an organization to give input on the points of information for a key information section in the SmPCs.

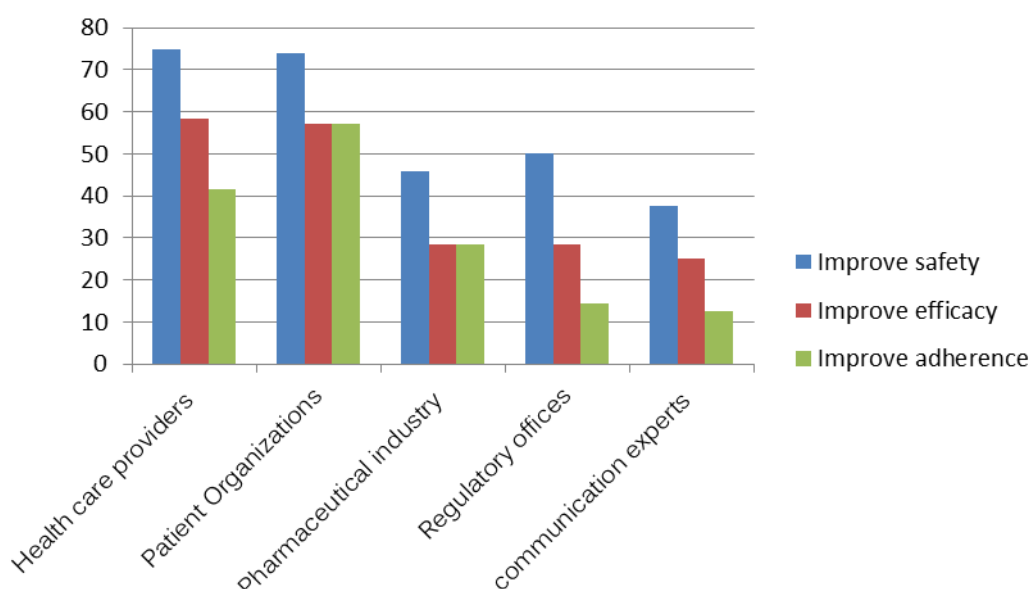


4.3.5 Potential positive and negative effects of a key information section

A first potential positive effect of adding a 'key information section' presented is that it would be read by people who would not read the PIL otherwise. Most participants agree on this (83% HCP, 76% Patient organizations, 56% Pharmaceutical industry).

Respondents were asked (open question) to name potential advantages and disadvantages of a key information section. Most respondents mentioned as a main advantage that people, who would otherwise not read the leaflet at all are probably more likely to read the key information section, which is important because then they have at least some information about their medication. As one respondent (health care provider) said: "*Important safety information can be accessed 'at a glance'*". Another quote reads: "*Better exposure of key information, less neglect, stronger recall* (communication expert).

Figure 4.9: Percentage of participants that think that a key information section could affect safety, efficacy and adherence positively.

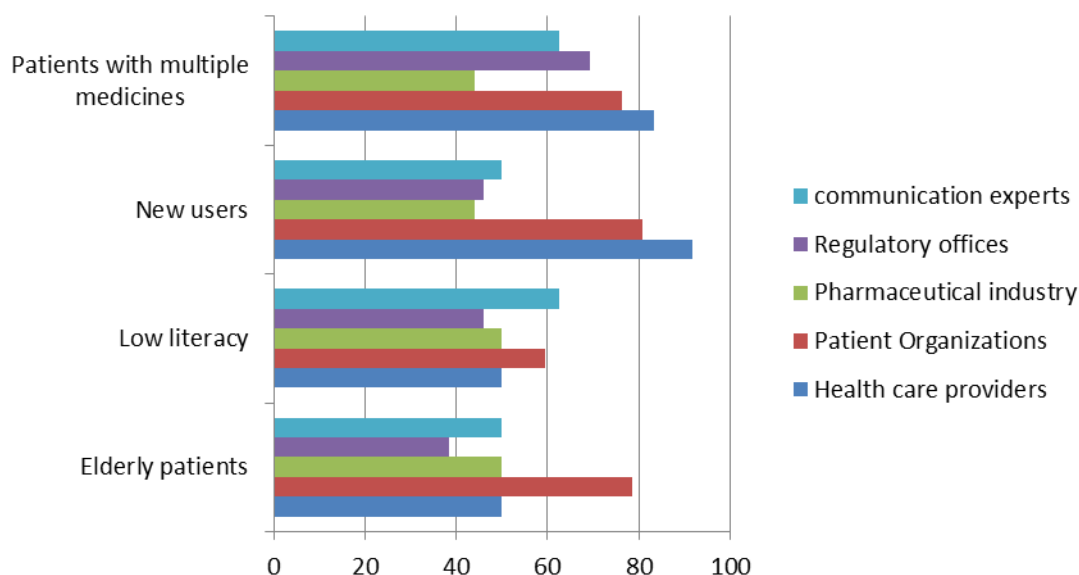


A majority of the HCPs and patient organization representatives think that a key information section can positively affect the safety of medicine use, as do half of the regulatory officers (Figure 4.9). The pharmaceutical industry representatives and communication experts are more sceptical. With the exception of patient organization representatives, a minority of all groups think that a key information section can affect the efficacy of medicine use and patients adherence to medication.

Potential disadvantages that were mentioned included that a key information section would lengthen a PIL or SmPC and that issues may arise around what information should be included and what information excluded. Moreover, the main advantage as described above is also mentioned by some respondents as a disadvantage: when people read only a key information section they could miss other important information that is in the main text.

Some more questions were asked about the positive and negative points of a special section for key information, especially when it comes to vulnerable groups of patients (such as the elderly and low literate patients) and reading the PILs by patients (Figure 4.10). Health care providers and patient organizations do foresee an added value of a key information section for new users of a particular medicine as well as for patients with multiple medicines. To a lesser extent both groups foresee some added value of a key information section for patients with low literacy and elderly patients. Pharmaceutical industry representatives foresee some added value of such an information section for all four groups of vulnerable patients and target groups. Added values that were named; *'if people have more information they are more likely to make informed decisions about their medicine taking'*. Or: *'Warnings could have a good effect on safety'*, according to a health care professional.

Figure 4.10: percentage of participants in favour of thinking that there is added value of a key information section for vulnerable patients.



4.3.6 Alternatives for a key information section

Respondents were also asked about possible alternatives to a key information section. Figure 4.11 shows that most respondents chose bolded text or text boxes in the main text, when it comes to alternatives in the PILs. Pharmaceutical industry representatives are most in favour of bolded text to make important information stand out for the main text. Especially regulatory offices are in favour of text boxes in the main text to highlight the key information. Yet, communication experts do not favour any of these possibilities.

When it comes to alternatives for the key information section in the SmPCs, bolded text and text boxes in the main text are also favourite (Figure 4.12). Still, the communication experts are in favour of options other than bold text, different colours in the text or text boxes in the main text.

Figure 4.11: percentage of participants in favour of an alternative for a key information section in PILs.

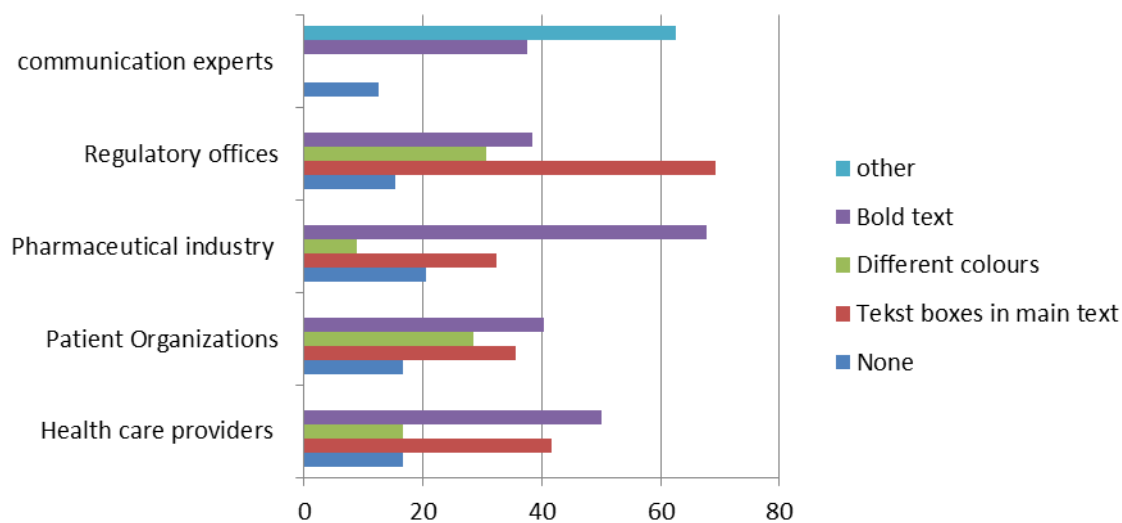
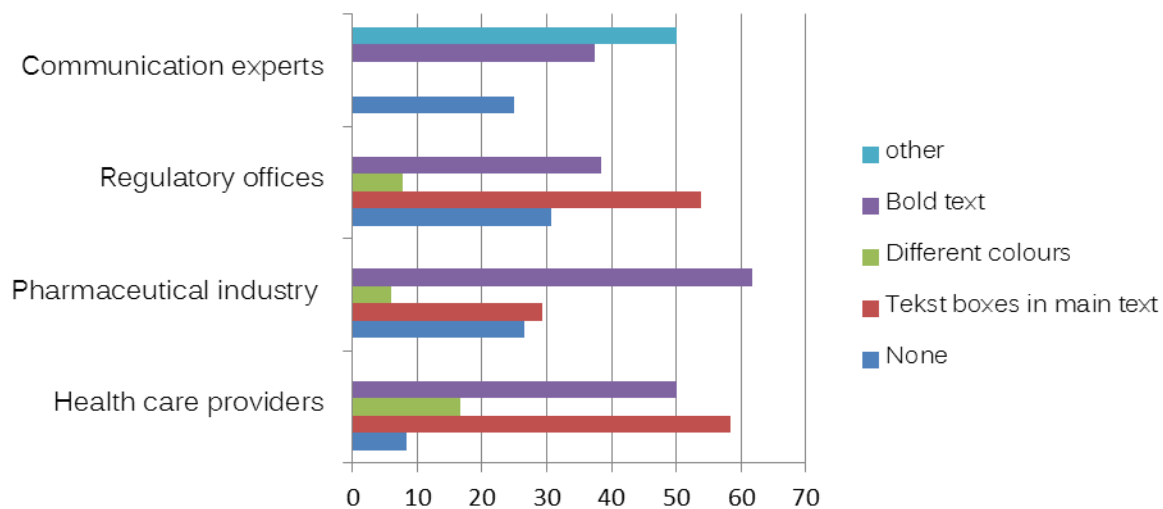


Figure 4.12: percentage of participants in favour of an alternative for a key information section in SmPCs.



4.3.6 Three examples of a “ key information section”

Finally, we showed the respondents three examples of key information sections for PILs with different lay outs and asked respondents which one they preferred.

Example A

Paroxetine 20mg and 30mg film-coated Tablets

Patient Information Leaflet

Important things you need to know about Paroxetine

Read all of this leaflet carefully before you start taking this medicine.

- Paroxetine treats depression and anxiety disorders but it will not work straight away. Like all medicines, it can have side-effects. It is important that you and your doctor talk about the benefits and the possible unwanted effects of the medicine before you start taking it.
- Paroxetine must not be taken by children or teenagers under 18. (See **Section 6** on page 4).
- Paroxetine will not work straight away. You may feel worse before feeling better after starting the medicine. Your doctor should ask to see you again 2 or 3 weeks after you first start taking the medicine. Tell your doctor if you feel no better. (See **Section 3** on page 2).
- Some people with depression or anxiety think of harming or killing themselves. If you have any of these thoughts, see your doctor or go to a hospital straight away. (See **Section 2** on page 1).
- If you feel restless or feel like you cannot keep still, go to your doctor. If you keep on taking more paroxetine each day, it may make these feelings worse. (See **Section 4** on page 3).
- Talk to your doctor before you stop taking paroxetine. If you stop taking it suddenly or miss a dose you may get unwanted effects. (See **Section 5**, on page 3).
- Taking some other medicines with paroxetine can cause problems. You may need to talk to your doctor first. (See **Section 2** on page 2).
- If you are pregnant or planning to get pregnant, talk to your doctor before taking paroxetine. (See **Section 2** on page 2).

Source: www.drugs.com/uk/pdf/leaflet/239073.pdf

Example B

PAXIL[®]

(paroxetine hydrochloride)

Tablets and Oral Suspension

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL is not approved for use in pediatric patients. (See **WARNINGS: Clinical Worsening and Suicide Risk**, **PRECAUTIONS: Information for Patients**, and **PRECAUTIONS: Pediatric Use**.)

source: FDA website (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020031s067,020710s031.pdf)

Example C

Medicine Information Box
Active ingredient
Glucosamine sulfate sodium chloride complex 1886 mg (equivalent to glucosamine sulfate 1500 mg) Chondroitin sulfate-bovine sodium 95% 842 mg (chondroitin sulfate sodium 800 mg)
Uses
<ul style="list-style-type: none">• May help to relieve osteoarthritic joint pain• Helps reduce cartilage wear• Chondroitin provides nutrition to the joints
Warnings and allergy information
<ul style="list-style-type: none">• Glucosamine is derived from seafood. Not recommended for people with seafood allergies• Contains approximately 228 mg sodium per daily dose• May occasionally cause mild gastrointestinal symptoms• Check with your doctor or pharmacist if you are taking any other medications
When using this product
If pregnant or breastfeeding, ask a health professional before use Keep out of reach of children. In case of overdose, seek medical attention or call the poisons information line on 13 11 26
Directions
Adults - Take 1 easy to swallow tablet twice daily with meals or as professionally prescribed Children under 12 years - Only as professionally prescribed. If symptoms persist, see your healthcare professional
Storage information
White, vanilla flavoured tablet with easy to swallow coating. Store below 30C. Protect from moisture

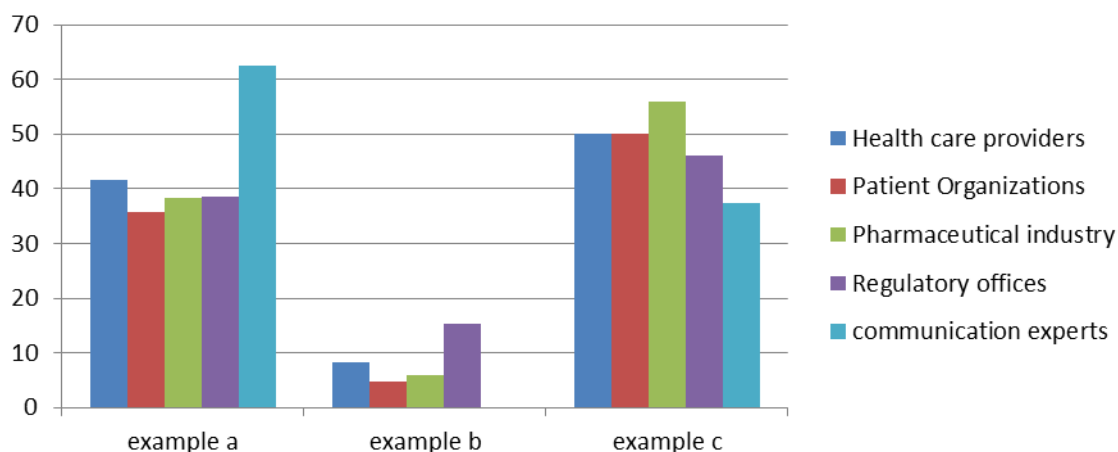
Source: TGA website
(<http://www.tga.gov.au/pdf/consult/consult-labelling-packaging-review-120524.pdf>)

Figure 4.13 shows that example C was the favourite for most participants, followed by example A. Respondents were also asked to briefly explain why they picked that particular example as their favourite. Most respondents chose example C because:

- *'it is best written and structured';*
- *'the lay out is better, it is clearer with a narrower column which makes it easier to scan and the headings a clear'.*

One respondent that chose example A said that *"it is easier to read, example B has too much text and example C seems to be broken up by the large headings"*.

Figure 4.13: Percentage of all participants in favour of an example PIL.



4.4 Results Online discussion forum

Box 4.1 shows the text and questions put on the online forum on the key information section.

Regarding the addition of a key information section, the following pro and cons were mentioned in the online discussion.

Pros:

Arguments mentioned in favour of adding a key information section included:

- Thus would allow to reduce the information in the PIL to key messages only and provide the rest through other channels (CE)¹².
- It could help people assimilate the most important information about their medicines and allow them to then be signposted to more detailed information within the body of the leaflet or elsewhere; Combining this with an electronic offering could mean that the information could be more readily personalised (RO).
- When the information in such section would be updated with important new safety information this which will help those people on chronic medication to know quickly whether there is anything new about which they should be aware (RO).

Cons:

There were also arguments mentioned opposing to a key information section:

- There is no evidence yet on the added value of a key information section and extensive testing is needed (CE).
- Space used to include such a section would make PILs longer than they are now (CE, RO, PI) and which may have technical and practical impacts (PI).

¹² CE =communication expert, RO=regulatory officer; PI=pharmaceutical industry

-
- It is difficult to standardize the content of a key information section, since medicines are different and also needs of different patient groups are different (PI).
 - Patients may be deterred from reading the rest of the PIL, if read at all (PI, RO).
 - It hard (and subjective) to define what “key information” is, which may trigger long legal discussions with the pharmaceutical industry (PI).

Suggestions

Finally, some suggestions were put forward by the participants to the online discussion:

- User testing of key information section is required (CE).
- It could be beneficial to provide only the most important information in a credit-card sized document within the pack with a link to the detailed information via an electronic web-link (RO).
- Looking for other ways to make sure that key information is being picked up, e.g. by making all information easily navigable and searchable (electronic tools) (PI).
- The order of sections to be expressed in the PIL is often commented upon by patients as a result of patient consultation and a different order may be recommended (PI).
- A true and radical reconsideration of the structure, content, layout and mode of dissemination of the PIL in its entirety, to refocus it to the needs of the patient, may be a more appropriate way to proceed (PI).
- More beneficial to the patient would be clear headings/sections, highlighted appropriately, which allow the patient and/or the HCP to easily locate the information that is important and relevant to their particular situation (PI).

Box 4.1 Questions regarding a key information section posed in the online discussion forum

Introductory text: In 2008 the European Commission adopted a legislative proposal containing several provisions related to the content the PILs. One of these provisions referred to the potential introduction of a “key information section”, allowing patients and health care professionals to rapidly identify key safety messages balanced with information on the benefits of medicines.

- **Question 1:** To what extent do you think that a key information section can be of added value for patients? What patients could benefit the most (new users of a medicine, chronic users, patients with co-morbidities, patients taking multiple medicines, elderly patients, low educated patients, others).
- **Question 2:** What key safety messages do you think should be stated in a key information section that would allow balancing risks and benefits of medicines?

4.5 Summary

The stakeholder consultation described in this chapter shows that stakeholders differed in their opinion as to whether or not to add a key information section to the PIL and SmPC. While the potential users (representative of patients and HCPs) were generally in favour of adding a key information section, the pharmaceutical industry and the regulatory officers were generally not.

With regard to the preferred lay-out of a key information section, a majority of all stakeholders seems in favour of adding the section in a text box at the beginning of the PIL/SmPC. A large majority of all stakeholders considers the following topics of relevance for the key information section: warnings, contra indicated illness and serious side effects. Overall, a minority of stakeholders is in favour of adding benefit information to a key information section. A majority of stakeholders agree that the number of issues addressed in a key information section should be limited. Cross-referencing is widely supported among all stakeholders, although there is no agreement on whether or not all information should be cross-referenced and how it should be done.

Most participants agree that adding key information section may lead people who would not read the PIL otherwise to at least read this section. However, the other side of the coin is that adding such section may also discourage patients from reading the whole leaflet. Furthermore, a majority of the HCPs and patient organization representatives think that a key information section can positively affect the safety of medicine use in a way, as do half of the regulatory officers. Pharmaceutical industry representatives and communication experts are more sceptical. With the exception of patient organization representatives, a minority of all groups think that a key information section can affect the efficacy of medicine use and patients adherence to medication.

Overall, the stakeholders' consultation shows that there is no clear consensus among different stakeholders as to whether or not to add a key information section to the PIL and SmPC, how such section should look like and what information it should contain. The lack of sound scientific evidence with regard to the added value of key information sections may be a reason for this.

Chapter 5 SWOT analysis

5.1 Introduction

This chapter provides a SWOT analysis of the potential added value of a key information section for the PIL and the SmPC. This SWOT-analysis will present strengths and weaknesses of adding a key information section for the safety and efficacy for medicines' use. It should be noted beforehand that evidence in the literature proved to be very limited (see chapter 3). Additionally, the stakeholder consultation showed that there is no clear consensus among different stakeholders as to whether or not to add a key information section to the PIL and SmPC, how such section should look and what information it should contain. However, there was a difference between the patient organisations and health care providers on the one hand (86% and 67% in favour of a key information section in all PILs) and pharmaceutical industry (33%) and regulators (12%). Moreover, the stakeholder consultation cannot answer questions on the efficacy and effectiveness (and costs) of adding a key information section. The intention was to perform two SWOT-analyses: one for the PIL and one for the SmPC. As the results for both documents were largely comparable one analysis was drawn up.

The SWOT analysis was drafted by the whole research team (MV, SM, SvdB, TR & LvD). They first studied the results and came together afterwards for a discussion that took one morning to identify strengths, weaknesses, opportunities and threats. It was further extended and discussed (by mail) by three members of the team (MV, LvD, TR). The SWOT analysis was based upon the results from the literature, the stakeholder consultation and the online discussion forum.

5.2 SWOT-analysis

Box 5.2 shows the SWOT-table. Below, we will discuss the two main weaknesses and one main strengths which arose, along with the opportunities and threats. Other arguments are shown in Box 5.2.

Weakness 1: too limited evidence

First and foremost, the main conclusion from our analysis is that there is ***too limited scientific evidence*** for the added value of a key information section so far in the literature, which is a weakness when deciding to introduce a key information section.

Related threat: In case a key information section were introduced now – there is a lack of testing on:

- whether or not such section has added value;
- what added value it can have;
- how such section could be composed best;
- what information should be included.

Weakness 2: No agreement on what information to include

The second weakness is that it is not yet clear what information should be included in a key information section. For example, while the limited number of scientific studies suggest that patients want a more balanced view on risks and benefits of their

medication when informed about the benefits as well¹³, the stakeholder consultation showed that a minority of stakeholders is in favour of adding such information to a key information section.

Related threat: The division among stakeholders on what information should be included in the key information section could be a threat in the development process of a key information section.

Related opportunities:

- Developing criteria for information to be included in a key information section. Based upon experiences with examples of key information sections in existence. Especially, the headline sections in the UK and the accompanying guidelines are of interest. Yet, only few results are available on the added value of these sections.
- Piloting and testing of such headline sections in other member states of the EU could be undertaken. The focus could be high risk medicines, as has been largely the case in the UK. A key outcome measure for such testing should be: is the net effect that more readers read some of the leaflet; and does that outweigh the number of patients who may no longer read some or all of the leaflet. Different piloted examples could focus on different aspects related to layout and to content.

Strenght 1: Positive attitude patients and HCPs towards adding a key information section

Patients and HCPs are those users who have been shown to have a positive attitude towards adding a key information section. This picture arises both in the limited body of literature and our stakeholder consultation.

Related threats:

- Those who are responsible for composing and approving the PIL and SmPC (the pharmaceutical industry and regulators) are more divided. They fear that costs for developing and PIL or SmPC becomes more expensive (weakness).
- While most stakeholders agree that special patient groups can be served by a key information section, there is also some concern that patients who now read the PIL, will only focus on the key information section .

¹³ This has not been tested specifically in key information sections.

Box 5.2 Result of SWOT analysis regarding the potential adding of a key information section to the PIL and SmPC

Strengths	Weaknesses
Evidence from the literature	
<p>No negative experiences so far reported in the literature</p> <ul style="list-style-type: none"> In the few studies that have been performed on adding a key information section to the PIL and SmPC there is no evidence that any harm has come from including a key information section and that users were positive about such section. 	<p>Too limited scientific evidence</p> <ul style="list-style-type: none"> Hardly any studies are available on the impact of key information sections with the exception of Black Box Warnings As such, scientific evidence on key information section is too limited to draw final conclusions on the added value of a key-information section as.
<p>@Benefit information associated with better benefit-risk evaluation of patients</p> <ul style="list-style-type: none"> Adding benefit information to patient informative can aid informed decision making as patients' knowledge about medication increases and patients better evaluate the risk-benefit balance of a medicine 	<p>No evidence on adding benefit information in key information section</p> <ul style="list-style-type: none"> No studies have been performed on key information sections including benefit information
<p>Examples of key information sections & accompanying guidelines exist</p> <ul style="list-style-type: none"> Examples exist of which the UK and Australian examples were evaluated positively. The UK headline section included both risk and benefit information and guidelines to compose such section are developed 	<p>UK example hardly tested in scientific research yet</p> <ul style="list-style-type: none"> Hardly any studies are available on the impact of key information sections
Evidence from stakeholder consultation	
<p>Target population in favour of key information section</p> <ul style="list-style-type: none"> The vast majority of patient organization representatives (93%) is in favour of adding a key information section to all or a selected number of PILs The vast majority of HCP representatives (91%) is in favour of adding a key information section to all or a selected number of SmPCs (NB: not that this is based on small numbers) Evaluation of alternatives for the key information section is contradictory among the target population 	<p>No clear support from industry and regulatory offices</p> <ul style="list-style-type: none"> Pharmaceutical industry representatives are divided about the introduction of a key information section to the PIL (40% is against) and SmPC (33% is against) Regulatory officers are divided about the introduction of a key information section to the PIL (30% is against) and SmPC (58% is against)

<p>Consensus about including risk information, but...</p> <ul style="list-style-type: none"> There is consensus (> 70% of the stakeholders) on at least including risk information in the key information section as it could contribute to a safe use of medicines. 	<p>.. no consensus on what other information to include in a key information section</p> <ul style="list-style-type: none"> Except for the inclusion of risk messages, there is no consensus regarding what information should be included in a key-information section.
<p>Patients may benefit...</p> <ul style="list-style-type: none"> A majority of the stakeholders believe that a key-information section is of added value for the majority of patient groups, with the exception of patients with low education. A majority of the stakeholders (69%) think that adding a key information section may increase the number of people who read some information 	<p>... or not?</p> <ul style="list-style-type: none"> The presence of a key information section may lead some people who previously read most of the leaflet to just read the key information section (open answers in survey and online discussion forum)
<p>Opportunities</p>	<p>Threats</p>
<ul style="list-style-type: none"> There is the opportunity to use the existing examples of key information sections (in use in UK and Australia) as well as the guidelines developed in the UK as a starting point to develop a template that would fit patients' needs. By adding a structured key information section, the current structure of PILs and SmPCs could be improved as well Patients representatives do not mind a longer PIL as long as it makes the PIL more clear (see Monteiro et al 2013). 	<ul style="list-style-type: none"> Lack of testing regarding the introduction of a key information section as there could be the risk of rushing to quickly into conclusions without actually testing the added value of a key information section. Risk that stakeholders do not agree upon what information should be included in KIS in general or in KIS for specific medicines Development of a template concerning the content of a key information section will not be supported by the ones responsible for the regulation of PILs/SmPCs Some people who previously read most of the leaflet to just read the key information section (which does not contain all information)

5.3 Summary

The SWOT-analysis presented in this chapter reveals that a weakness for introducing a key information section to the PIL and SmPC is the limited evidence for the added value of such a section. However, an important strength is that patients and HCPs, who would be the users of such a section, have been shown to have a positive attitude towards adding a key information section. A second weakness is that it is not yet clear what information should be included in a key information section and the division among stakeholders on what information should be included could be a threat in the development process of a key information section. And while most stakeholders agree that special patient groups can be served by a key information section, there is also some concern that patients who now read the PIL, will only focus on the key information section.

Chapter 6 Summary and conclusion

6.1 Introduction

Background

In 2008 the European Commission adopted legislative proposals to strengthen and rationalise pharmacovigilance in the EU. These proposals contained several provisions related to the content of the Package Information Leaflets (PILs) for patients and the Summaries of Product Characteristics (SmPC) for professionals. One of these provisions referred to the introduction of a new section in the PIL and SmPC on 'key information'. Such a section would allow patients and health care professionals to rapidly identify key safety messages, balanced with information on the benefits of medicines. In view of this, the Commission asked for an assessment on the added value of such section. This assessment is provided in this report.

Main objectives of the study

The objective of this study is to provide the European Commission with an assessment of the current evidence with regard to:

- the potential effects of the introduction of "key information" sections to rapidly identify key safety messages balanced with information on the benefit of medicines in patient information leaflets (PIL) and Summaries of Product Characteristics (SmPC);
- the feasibility of such a tool in the context of the European Union legislation on authorisation of medicinal products for human use.
- to assess the potential cost/efficacy of adding a key information in the context of the EU legislation.

To accomplish this assessment, three tasks were undertaken:

- an extensive literature search
- a consultation of the relevant stakeholders,
- an analysis to evaluate the Strengths, Weaknesses, Opportunities and Threats (SWOT).

In the next two sections the main findings from the literature search and the stakeholder consultation will be summarized. After that we will reflect upon the methods used and in the last section we will provide final conclusions and recommendations.

6.2 Main findings literature survey

A literature survey was conducted to gather evidence on: (1) the inclusion of a key information section with regard to the safety and efficacy of medicines' use, (2) the identification of what is key information and (3) the feasibility of introducing a key information section. A comprehensive literature search was conducted in the following electronic databases PubMed, Embase, Sociological Abstracts and Communication and

Mass Media Complete and using snowball techniques afterwards. This resulted in 23 studies mainly on US Black Box warnings, which are solely about safety issues, and go against the strong evidence that patients want a balance of benefit and harm information. In addition to the electronic databases covering scientific literature, a search of the grey literature was conducted in the following repositories: Digital Repository Infrastructure Vision for European Research (DRIVER) and Scirus and on relevant websites. The main findings are described below.

Examples of key information sections are available, but literature includes limited evidence on the added value

In the UK (headline section), Australia (medicine information box) and the US (Drug Facts box and Black Box Warnings), a type of key information section is already in use or proposed, albeit on the package label (in Australia and the US), rather than in the PIL. The Drug Facts box developed for inclusion in direct-to-consumer advertisement also presents a format for balanced benefit/harm medication information. Thus, these examples might be useful as a basis if a key information section was to be developed. Yet, while the number of examples of key information sections seems to be growing, the evidence on the added value of a key information section is limited, especially when it concerns key information sections combining risk and benefit information. Most evidence is available for black box warnings in the US, showing that those warning generally decrease the medication's use. However, the European Commission is more in favour of potentially adding a key information section that includes both risk and benefit information. The only study on adding a key information section also including benefit information to the PIL concluded that *the headline section did not influence 'findability' or comprehension of information in the PIL*. Furthermore, the PIL with the headline section was perceived to be as difficult, well designed and useful as a PIL without this section. Yet, participants were enthusiastic about the section and thought it was an improvement to the PIL. The only (qualitative) study on adding key information to the SmPC found a positive attitude of professionals in a user test.

Patients have a better understanding of the benefit-risk ratio after reading benefit information

Evidence on including benefit information in patient information shows that this information increases patients' knowledge about the medicine and their judgment (e.g. effectiveness of the medicine, its benefit to health and their satisfaction with the provided information) of the medicine.

United Kingdom recently introduced key information (headline) sections accompanied by guidelines

The only country in the European Union where key information sections (headline sections) are used is the United Kingdom (UK) following a report by the MHRA. This report recommended the following to improve patient information leaflets: include a headline section, provide balanced information and provide better information on side effects. The MHRA developed guidelines on these issues. This guideline proposed by the MHRA might be useful for deciding on which information to be included in the key information section and how to present this information, as well as design aspects. Still, the need for user testing remains. Currently, only two studies testing these headline sections have been performed, one on the PIL and one on the SmPC.

Overall, it can be concluded that there is little evidence available yet for the added value of including a key information section with balanced information on the benefits and the risks of the medication in the PIL and/or SmPC let alone for its feasibility and cost-effectiveness. Experiences and guidelines from the UK can be helpful for further developments at the EU level.

6.3 Main findings from the stakeholder consultation

The next phase of the study was a stakeholder consultation to retrieve the opinions of relevant stakeholders on potentially adding a key information section to the PIL and the SmPC such as: (1) what information can be identified as 'key' information for a special section in the PIL and SmPC; (2) What are the challenges of adding a key information section in PIL and SmPC, (3) what are the positive and negative effects of a key information section on PIL and SmPC and their value for their respective users? and (4) how do they value potential alternatives for a key information section? A structured online questionnaire was developed in order to capture stakeholders' views on the key information section. These questionnaires were sent out to different stakeholders. Afterwards an online discussion was held with a smaller number of participants.

Participants

Although numerous actions were undertaken to approach European and national representatives of stakeholders the response to the survey was limited: 119 respondents overall participated in the survey. Stakeholders included patient organizations, health care professional organizations, pharmaceutical industries, regulatory officers, and communication experts. Participants represented a wide variety of countries in the EU, with an overrepresentation for the UK, the Netherlands, Sweden and Belgium. Most participants worked in national organizations.

In total 20 participants were involved in the online discussion: two representatives of European level patient organizations, three representatives of health care professional organizations, 4 regulatory officers, 7 experts on communication in the PIL and 5 representatives of the pharmaceutical industry.

Adding a key information section

The first question is whether stakeholders are in favour of adding a key information section at all. There was a rather clear division among stakeholders on this. While the potential users (representative of patients and HCPs) were generally in favour of adding a key information section, the pharmaceutical industry and the regulatory officers were generally not.

Lay-out and content of a key information section

With regard to the preferred lay-out of a key information section, a majority of all stakeholders seems in favour of adding the section in a text box at the beginning of the PIL/SmPC. A large majority of all stakeholders (except communication experts) considers the following topics of relevance for the key information section: warnings, contra indicated illness and serious side effects. Overall, a minority of stakeholders is in favour of adding benefit information to a key information section (except communication experts). A majority of stakeholders agree that the number of issues addressed in a key information section should be limited to between 5 and 10. Cross-referencing is widely supported among all stakeholders, although there is no agreement on whether or not all information should be cross-referenced and how it should be done.

Perception of positive and negative effects

Most participants agree that adding key information section may lead people who would not read the PIL otherwise to at least read this section. However, the other side of the coin is that adding such section may also discourage patients from reading the whole leaflet. Furthermore, a majority of the HCPs and patient organization representatives think that a key information section can positively affect the safety of medicine use in a way, as do half of the regulatory officers. The pharmaceutical industry representatives and communication experts are more sceptical. With the exception of patient organization representatives, a minority of all groups think that a key information section can affect the efficacy of medicine use and patients adherence to medication.

Alternatives for a key information section

Most respondents chose bolded text or text boxes in the main text as an alternative for a key information section in the PIL, but pharmaceutical industry representatives are most in favour for bolded text to make important information stand out from the main text. In our related study on the readability and comprehensibility of the PIL, it was suggested to explore the added value of electronic formats next to the paper version of the PIL (Van Dijk et al 2014). The added value of a key information section could be explored in such additional electronic formats.

Conclusion

Overall, the stakeholders' consultation shows that there is no clear consensus among different stakeholders as to whether or not to add a key information section to the PIL and SmPC, how such section should look like and what information it should contain. The lack of sound scientific evidence with regard to the added value of key information sections may be a reason for this.

6.4 Limitations of the study

The number of studies we found on key information sections were very small. As a result, little evidence could be derived. Although we did a thorough search in both the scientific literature as well as in search engines for grey literature we may have missed grey studies which were not documented. We have approached ministries in our earlier study (see Monteiro 2013) and asked for their input but received a limited response. Therefore, we did not use this approach again.

The idea was to base the stakeholder questionnaire on the evidence found in the literature. As the literature provided hardly any evidence, the stakeholder questionnaire has been drawn up based upon the expertise from the research team, one of whose members is an expert on patient and professional information on medicines (DKTR) and who was involved in the committee drawing up the report "Always read the leaflet" (MHRA 2005).

Stakeholders in all EU Member States as well as from other European countries were given the opportunity to reflect on the potential value of a key information section 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 as questionnaires were only provided in English. This may be the reason that countries from 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. Therefore, the results of these stakeholders had to be cautiously interpreted and no strong conclusion can be derived.

6.5 Conclusions and recommendations

This report describes an assessment of evidence with regard to adding a section containing key information to Package Information Leaflets (PILs) and Summaries of Product Characteristics (SmPC) of medicines. The main conclusion of this assessment is that scientific evidence on the added value of such a section is very limited and is inconclusive so far. This conclusion is based on the lack of evidence found in the scientific literature¹⁴ although, in the few studies of a key information section in a PIL or SmPC, there is no evidence that any harm has come from including a key information section and users were positive about such section. In addition, there are generally mixed opinions different stakeholders have on adding a key information section to PIL and SmPC, how it should look like and what information it should include. However, it should be noted that patients' organisations and health care professionals are generally positive about the addition of such a section, and that the pharmaceutical industry and regulators are generally more negative about this.

There remain three key unanswered questions from the literature and the mixed evidence found in the stakeholder consultation:

1. What is the appropriate format and positioning of a key information section?
2. How many points should be included and how should the included points be decided upon?
3. Does a key information section **on balance** lead to a more informed, and therefore safe and effective, user of the medicine i.e. are the number of new readers of the PIL, as a result of the key information section, greater than the number who no longer read the whole leaflet – and just read the key information section?

Additionally, the above investigations have not covered the point that the two documents are separate documents but they are linked. At present, the PIL is based upon the SmPC, and so a key information section in the latter would shape such a section in the latter. This assessment showed that the information prescribers want and need in a key information section is not necessarily the same as patients want and need. As such, there is lack of evidence regarding whether or not a key

¹⁴ Only for Black Box Warnings evidence was found on the effect it had on medication use. However, these BBWs have a different goal than the key information section as anticipated in the EU.

information section has added value for patient understanding and patient safety, on how such sections should ideally be composed and what information should be included. In addition, there is no information on its cost efficacy.

Legal justification may come from the provisions of article 62 of Council Directive 2001/83/EC which allows the inclusion of other information which is useful for the patient, consistent with the SmPC and being non- promotional.

EU-wide user testing needed

Evidence can be built in different ways. The first way is to learn from the UK experience, where there are several PILs with a key information section (headline section). These are constructed based upon guidelines proposed by the MHRA in 2005. In the upcoming few years more evidence could be gathered on the added value of these sections. This evidence may guide further developments at the EU-level. The EU could facilitate studies in the UK on scientifically testing the key information section. Moreover, in case a key information section were to be added testing is recommended. Such testing should focus on different types of key information sections, in terms of lay-out and especially in terms of content. The reason for this is that it is not yet clear what information should be included from the literature and also different stakeholders do not agree upon the issues to be included with the exception of risk information. User testing should not only focus on the comprehensibility of the information but also on whether the information fits to users' and on whether or not users read information other than the key information section, for example as guided by cross-referencing.

Recommendations

Based upon the above the following recommendations are made:

1. Do not introduce a key information section as a mandatory requirement, bearing in mind the current level of evidence.
2. Allow the use of key information sections in PILs which have been user tested with a particular focus on the key information section. This will help gather more evidence on what such section should look like and what information it should include.

In order to further facilitate an introduction of such a section in the future, the following recommendations are made:

3. Retrieve and stimulate evidence from the implementation of headline sections in the UK.
4. Facilitate EU-wide evaluation of a variety of key information sections, preferably on high risk medicines, on selected PILs and SmPCs, through user testing and wider research.
5. Develop criteria for the inclusion of points of information in these sections based upon further surveying of the stakeholders (primarily patients and health professionals) and the outcome of the above testing.
6. Explore the development and impact of key information sections first in electronic versions of the PIL and SmPC.

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Directives and regulations

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Directive 2010/84/EU
Regulation No726/2004
Regulation (EU) No 1235/2010

Appendix 1 List of excluded studies in the literature survey 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 and includes information on a key information section or potential alternatives;
- (2) The publication refers to the evidence with regard to subjects to be included in a key information section, the safety and efficacy of medicines' use, the feasibility of the inclusion of key information section (including success factors as well as potential negative consequences of a key information section and/or cost efficacy);
- (3) In case a publication is not in one of the four main languages of the EU (English, German, French or Spanish) or in a language mastered by the research team (Dutch, Portuguese), it needs to contain a summary (which can be translated in English);
- (4) 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	1998	Beach JE, Faich GA, Bormel FG, Sasinowski FJ	Black box warnings in prescription drug labeling: results of a survey of 206 drugs	Criteria (2) not met
PubMed	2001	Drug Therapeutic Bulletin; Consumers Association	Failings in treatment advice, SPCs and black triangles	Criteria (1) and (2) not met
PubMed	2002	FDA	New OTC drug facts label	Criteria (4) not met <i>grey literature</i>
PubMed	2002	van Grootheest AC, Edwards IR	Labelling and 'Dear Doctor' letters: are they noncommittal?	Criteria (1) and (2) not met
PubMed	2002	Weatherby LB, Nordstrom BL, Fife D, Walker AM	The impact of wording in "Dear doctor" letters and in black box labels	Criteria (1) and (2) not met
PubMed	2004	Wilkinson JJ, Force RW, Cady PS	Impact of safety warnings on drug utilization: marketplace life span of cisapride and troglitazone	Criteria (1) and (2) not met
PubMed	2006	Aaronson DW	The "black box" warning and allergy drugs	Criteria (2) not met
PubMed	2009	Busch SH, Barry CL	Pediatric antidepressant use after the black-box warning	Criteria (2) not met
PubMed	2009	Cook DM, Gurugubelli RK, Bero LA	Risk management policy and black-box warnings: a qualitative analysis of US FDA proceedings	Criteria (2) not met
PubMed	2010	Wang LM, Wong M,	Black box warning contraindicated	Criteria (2) not met

		Lightwood JM, Cheng CM	comedications: concordance among three major drug interaction screening programs	
PubMed	2011	Aikin KJ, O'Donoghue AC, Swasy JL, Sullivan HW	Randomized trial of risk information formats in direct-to-consumer prescription drug advertisements	Criteria (1) and (2) not met
PubMed	2011	Buckley NA, Rossi S	Bringing greater transparency to "black box" warnings	Criteria (4) not met (commentary)
PubMed	2011	Cheng CM, Fu C, Guglielmo BJ, Auerbach AD	Boxed warning inconsistencies between drug information resources and the prescribing information	Criteria (2) not met
PubMed	2011	Duke J, Friedlin J, Ryan P	A quantitative analysis of adverse events and "overwarning" in drug labeling	Criteria (1) and (2) not met
PubMed	2011	Musleh S, Kraus S, Bennett K, Zaharan NL	Irish Medicines Board safety warnings: do they affect prescribing rates in primary care?	Criteria (1) and (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	2011	Rahmner PB, Eiermann B, Korkmaz S, Gustafsson LL, Gruven M, Maxwell S, Eichle HG, Veg A	Physicians' reported needs of drug information at point of care in Sweden	Criteria (1) and (2) not met
PubMed	2011	Schwappach DL, Mulders V, Simic D, Wilm S, Thurmann PA	Patients' preferences for drug information leaflets	Criteria (1) and (2) not met
PubMed	2011	Sen EF, Verhamme KM, Felisi M, 't Jong GW, Giaquinto C, Picelli G, Ceci A, Sturkenboom MC	Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age	Criteria (1) and (2) not met
Embase	2010	Bennett CL, Adegboro OS, Calhoun EA, Raisch D	Beyond the black box: Drug- and device-associated hypersensitivity events	Criteria (1) and (2) not met
Embase	2012	Singh RR, Nayak R	Atypical antipsychotic black box warning and its effect on nonantipsychotic psychotropic drugs in non-institutionalized dementia patients	Criteria (4) not met (abstract for symposium)
Embase	2012	Singh RR, Nayak R	Impact of FDA black box warning on the prescribing of atypical antipsychotics in non-institutionalized dementia patients	Criteria (4) not met (abstract for symposium)

Appendix 2. Excerpt from Always Read the Leaflet

Guideline on communication of risks and benefits in the PIL (taken from the report "Always read the leaflet", (25)).

A) HEADLINE INFORMATION

This section should focus on information that the patient must be aware of in order to ensure safe and effective use of his/her medicine.

General format

- i. Headline information should be at the beginning of the leaflet, presented so as to maximise its visibility and the likelihood of it being read. This might include highlighting the text or using a larger font size.
- ii. Information should be presented as a short series of bullet points. In most cases between 2 and 6 points should suffice; however, there is no "standard" length, and marketing authorisation holders will need to use their discretion in deciding upon the number and type of headlines. There may be some products for which no headlines would be necessary (for example, simple products for which there are no significant safety issues, such as aqueous cream).
- iii. Only the key messages on safe and appropriate use of the product should be included in this section. As a general principle, the section should be kept short in order that patients do not rely on it as a substitute for reading the main body of the PIL.

Most suitable types of information for inclusion:

- iv. Manufacturers should consider which are the most essential messages, bearing in mind the product and its therapeutic context. Typically these may relate to:
 - why the patient should take the product;
 - the maximum dose or duration of treatment;
 - potential side effects/withdrawal reactions (symptoms to look out for, especially for common or serious side effects);
 - contraindications;
 - important drug interactions;
 - circumstances in which the drug should be stopped;
 - what to do if the medicine doesn't work;
 - where to find further information.
- v. "Positive" information on the anticipated benefit of taking the medication should be included (usually as the first bullet point) in order to provide balance and context for the "negative" information referring to possible adverse events. Positive information should be limited to short factual statements stating the licensed indication (e.g. "Your doctor has prescribed [PRODUCT] because it is a treatment for X). Specific efficacy data or other product claims should not be included.
- vi. There should be a standard form of wording indicating that the patient should read the rest of the leaflet. The date of the latest revision of the leaflet should be stated, so that long-term users will be aware when there is a need to re-read the PIL.
- vii. Consistency across all products containing a particular drug substance and/or drug class is encouraged.

Less suitable types of information:

- i. Hypersensitivity (which is almost universally listed as a contraindication) except where it is a significant clinical issue e.g. penicillin.
- ii. Contraindications in uncommon conditions – specifically those which the patient would be expected to be aware of if they have the condition e.g. porphyria.
- iii. Precautions that are primarily relevant for the doctor's decision on whether to prescribe. For example, psychoactive drugs that should be prescribed with

- iv. Strict advice to avoid a medicine during pregnancy or lactation should only be included in the headline section if there are important safety data to support this recommendation.
- v. Undesirable effects and interactions that represent issues of tolerability rather than of safety (e.g. gastrointestinal upset, headache), or are unlikely to be of major clinical importance.
- vi. Advice relating to rare scenarios in which the patient would seek urgent advice (e.g. stroke, anaphylaxis, a first seizure) and where the advice in the PIL headline section would be unlikely to have any bearing on the action taken by the patient.
- vii. Overdose, unless a particular concern e.g. paracetamol.

A format is proposed with some example headlines:

Important things that you need to know about [PRODUCT]:

- Your doctor has prescribed [PRODUCT] because it is a treatment for X.
- If you are pregnant or could get pregnant you should talk to your doctor before taking [PRODUCT].
- Taking some other medicines with [PRODUCT] can cause problems. Tell your doctor if you are taking anything else (including herbal or "natural" remedies). If you are, you should read the section below on "taking other medicines" carefully.
- Do not take more than 4 tablets in 24 hours.
- Do not stop taking this medicine suddenly – you might get a reaction, such as...
- Most people don't get side effects taking [PRODUCT] but some people do – for example inflammation of the liver (hepatitis): see page 2 for more information.

Now read the rest of this leaflet. It includes other important information on the safe and effective use of this medicine that might be especially important for you. This leaflet was last updated on xx/xx/xx.

B) PRESENTING THE BENEFITS OF MEDICINES

A few sentences (about 80 words or fewer) should be sufficient to enable the necessary information to be included. This could be included in the section of the PIL entitled "What is your medicine and how does it work?". The information should be up-to-date, factual, informative and non-promotional. It might include some or all of the following:

- why it is important to treat the disease and what the likely clinical outcome would be if the disease remained untreated;
- whether the treatment is for short term or chronic use;
- whether the medicine is being used to treat the underlying disease (i.e. curative) or for control of symptoms. If the latter, which symptoms will be controlled and how long the effects will last;
- whether the effects will last after the medication is stopped;
- where the medicine is used to treat two or more discrete indications, all should be succinctly described as above;
- where to obtain more information on the condition.

Two examples are provided:

Example (1) - antihypertensive drug

With benefit info

PRODUCT belongs to a group of medicines known as angiotensin II receptor antagonists and is used to treat high blood pressure. High blood pressure often causes no symptoms, but if it is not treated it can damage blood vessels in the long-term. In some cases this can lead to heart attacks, kidney failure, stroke or blindness. That is why it is important not to stop taking this medicine without talking to your doctor.

Example (2) - inhaled steroid

With benefit info

PRODUCT contains beclometasone propionate which is one of a group of medicines called corticosteroids, or "steroids".

Without benefit info

PRODUCT belongs to a group of medicines known as angiotensin II receptor antagonists. This medicine lowers your blood pressure.

Without benefit info

PRODUCT contains beclometasone

Corticosteroids prevent attacks of asthma by reducing swelling of the air passages and are sometimes called "preventers". You should take this medicine regularly every day even if your asthma is not troubling you. Using PRODUCT can help prevent severe asthma attacks which sometimes need hospital treatment and if left untreated could even be life-threatening. This medicine should not be used to treat a sudden asthma attack – it will not help. You will need to use a different inhaler to deal with these attacks.

propionate which is one of a group of medicines called corticosteroids. These have an anti-inflammatory action and are used to treat asthma.

C) PRESENTING INFORMATION ABOUT SIDE EFFECTS

Describing side effects: order, seriousness and severity and dose

- a. Adverse drug reactions (ADRs) should be grouped in a manner that is meaningful for patients. In particular, grouping should allow easy identification of ADRs that mandate action, such as stopping treatment or seeking medical advice. These data should be provided with estimated risk frequencies (see below).
- b. Descriptions should convey both the nature and seriousness of possible ADRs. For example, reactions such as gastrointestinal bleeding or rhabdomyolysis can be life-threatening and this should be clear in the PIL. Where possible, symptoms should be provided.
- c. Where specific information on the severity of side effects is known this should also be included in the PIL (eg "headaches that may be severe or long lasting").
- d. Many side effects are dose-related. PILs should advise patients that higher doses, needed to achieve full benefit/efficacy in some patients, may be associated with an increased risk of side effects. A general warning statement may suffice in some circumstances, but care is needed to ensure that the warning is not alarmist to those who have been prescribed high doses. Specific statements relating to individual side effects may be appropriate if an important dose-relationship exists (eg muscle side effects with statins), or if there is a narrow therapeutic index.
- e. Consider providing links/details of further information sources on side effects.

Basic principles of describing statistical risk

- f. Quantifying risk: present risk numerically using absolute numbers, eg 1 in 10,000 patients. Convey baseline risk and absolute excess risks wherever possible.
- g. Verbal descriptors (eg "very rare") should only be used if accompanied by the equivalent statistical information. For example, "Very rarely (fewer than 1 in 10,000 patients treated)..."
- h. Point estimates: convey imprecision of point estimates using terms such as "approximately" / "about" / "around" when referring to estimates for major safety issues (eg "about 5 extra cancers for every 1000 patients treated").
- i. Frequency ranges: only refer to the upper bound for each range. For example, use 'fewer than 1 in every 1,000' rather than 'between 1 in 10,000 and 1 in 1,000'.
- j. Duration of risk: state the duration over which the excess risk applies if this is known. For example, the risk of agranulocytosis with clozapine is known to differ in the first 18 weeks versus weeks 19-52 and weeks 53 and above. If it is stated in the SPC that specific side effects may occur shortly after starting the drug and are likely to be transient, this information is helpful to include in the PIL.
- k. Frequency estimates based on spontaneous ADR data: reporting rates are likely to be an underestimate of true incidence or risk. This should be stated in the PIL when referring to data based only on spontaneous ADR data.
- l. Constant denominators: in some cases, it may be helpful to express the risk of adverse reactions using a 'constant denominator' in presentation of risk frequency, for instance when expressing small differences in risk (see below). This will not be appropriate in all circumstances.

Grouping of ADRs

It is particularly important that patients can easily identify the warning symptoms of potentially serious side effects that would necessitate action. Advice on necessary actions should be as specific as possible. These side effects and their respective probabilities should therefore be grouped together at the start of the side effect section. The following format is recommended:

"Important side effects or symptoms to look out for – and what to do if you are affected. If you think you may have any of the following side effects or symptoms, stop your medicine and see a doctor as soon as possible". (This wording should be adapted as appropriate to each product).

Appendix 3 Questionnaire online stakeholder consultation (patient version on key information sections)¹⁵

II PART – The “Key information section”

In 2008 the European Commission adopted a legislative proposal containing several provisions related to the content the Package Information Leaflets (PILs) for patients and the Summaries of Product Characteristics (SPC) for professionals. One of these provisions referred to the introduction of a “key information section”, allowing patients and health care professionals to rapidly identify key safety messages balanced with information on the benefits of medicines. These have also been described before as ‘Summary Information Boxes’ or ‘Headline Sections’.

This section of the questionnaire refers to your opinion on “key information sections”.

1. Are you in favour of including a “key information section” in PILs?
 - Yes, in all PILs
 - Yes, but only in selected PILs
 - No
 - a. Could you please briefly explain your answer?

Even if you are not in favour of adding a “key information section” in PILs, we would appreciate if you could fill in the following questions. Because your opinion matters to us.

2. Where in the PIL should a “key information section” be positioned?
 - At very beginning of the PIL
 - Between the *introductory bullets of the general information* and the *contents list*
 - Covering the front page of a folded leaflet, being the first thing you see when taking the PIL out of the package
 - Other place: _____
3. How should a “key information section” be highlighted to make it stand out?
 - In a text box
 - In a shaded box
 - Other: _____
4. What type of font should be used to highlight a “key information section”? *More than one option possible.*
 - Bigger font
 - Different colour
 - Bolded text
 - Other: _____
5. How would you like to have the information in a “key information section” organized?
 - In bullet points
 - In a paragraph form
 - Other: _____

¹⁵ Questions for other stakeholders were similar, including comparable questions on the SmPC.

-
6. Which of the following points do you consider relevant to be included in a “key information section”? *You may choose more than one category.*
- What the medicine is and what it is used for
 - Duration of treatment
 - Signs of the illness improving
 - Likelihood of benefiting from the medication
 - Significant contra-indicated illnesses
 - Significant warnings
 - Significant interaction with other medicines
 - Significant interactions with food and drink
 - Significant pregnancy, breast-feeding or fertility related information
 - Effects on the ability to drive or use machines
 - Brief description of the dose
 - Serious side effects requiring immediate action
 - Other: _____
7. The number of points will depend on the medicine but, in general, how many points of information should be included, in the “key information section”?
- up to 5,
 - 5 to 10,
 - 10 to 15,
 - more than 15
8. Do you think the information presented in a “key information section” should be referenced to the information in the main text (cross-referenced)?
- Yes, all points
 - Yes, but only points where there is further information in the main text
 - Yes, but only some points
 - No
- a. If *Yes, but only some points*, which points should be cross-referenced?
- b. If *yes*, how do you think the cross reference should be done?
- Graphical indicator e.g. ©, ✕, ¥ (or any other sign to link the section in the “key information section” with the main section in the PIL)
 - With text e.g. See “Pregnancy and breast-feeding” in Section 2
 - Both
 - Other: _____
9. Who should give input on the points of information to be included in a “key information section”? *More than option possible.*
- Regulators
 - Pharmaceutical companies
 - Independent pharmacists
 - Independent doctors
 - Patient organizations
 - Consumer organizations
 - Other: _____

10. Do you believe that the inclusion of a “Key Information section” would lead to:

	Yes	No	I don't know
People reading the Key Information section who would otherwise not read any of the leaflet.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
People only reading the Key Information section who would otherwise read the whole leaflet.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Make no difference to who reads what.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

-
11. In your opinion, what are the three main advantages of a “key information section”? *open question*
12. In your opinion, what are the three main disadvantages of a “key information section”? *open question*
13. Do you think a “key information section” could affect safety and efficacy of medicines’ use and patients’ adherence to medication?

	Yes	No	I don't know
Improve safety of medicines’ use	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Improve efficacy of medicines’ use	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Improve adherence to medication	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

a. Can you please briefly explain your answers?

14. What alternatives other than a “key information section” would you suggest to highlight important information in the PIL? *More than one option possible.*

- None
- Text boxes around pieces of information in the main text
- Use of different colours for pieces of information in the main text
- Use of bold text for pieces of information in the main text
- Other: _____

15. Can you foresee the added value of a key information section for the following more vulnerable patients or target groups?

	Yes	No	I don't know
Elderly patients	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Patients with low literacy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
New users of a medicine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Patients with multiple medicines	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other groups: _____	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

The following questions refer to 3 examples of “key information sections”. Please take some time to carefully look at the examples shown below.

Example A

Paroxetine 20mg and 30mg film-coated Tablets

Patient Information Leaflet

Important things you need to know about Paroxetine

Read all of this leaflet carefully before you start taking this medicine.

- Paroxetine treats depression and anxiety disorders but it will not work straight away. Like all medicines, it can have side-effects. It is important that you and your doctor talk about the benefits and the possible unwanted effects of the medicine before you start taking it.
- Paroxetine must not be taken by children or teenagers under 18. (See **Section 6** on page 4).
- Paroxetine will not work straight away. You may feel worse before feeling better after starting the medicine. Your doctor should ask to see you again 2 or 3 weeks after you first start taking the medicine. Tell your doctor if you feel no better. (See **Section 3** on page 2).
- Some people with depression or anxiety think of harming or killing themselves. If you have any of these thoughts, see your doctor or go to a hospital straight away. (See **Section 2** on page 1).
- If you feel restless or feel like you cannot keep still, go to your doctor. If you keep on taking more paroxetine each day, it may make these feelings worse. (See **Section 4** on page 3).
- Talk to your doctor before you stop taking paroxetine. If you stop taking it suddenly or miss a dose you may get unwanted effects. (See **Section 5**, on page 3).
- Taking some other medicines with paroxetine can cause problems. You may need to talk to your doctor first. (See **Section 2** on page 2).
- If you are pregnant or planning to get pregnant, talk to your doctor before taking paroxetine. (See **Section 2** on page 2).

source

Example C

Medicine Information Box
Active ingredient
Glucosamine sulfate sodium chloride complex 1886 mg (equivalent to glucosamine sulfate 1500 mg) Chondroitin sulfate-bovine sodium 95% 842 mg (chondroitin sulfate sodium 800 mg)
Uses
<ul style="list-style-type: none">• May help to relieve osteoarthritic joint pain• Helps reduce cartilage wear• Chondroitin provides nutrition to the joints
Warnings and allergy information
<ul style="list-style-type: none">• Glucosamine is derived from seafood. Not recommended for people with seafood allergies• Contains approximately 228 mg sodium per daily dose• May occasionally cause mild gastrointestinal symptoms• Check with your doctor or pharmacist if you are taking any other medications
When using this product
If pregnant or breastfeeding, ask a health professional before use Keep out of reach of children. In case of overdose, seek medical attention or call the poisons information line on 13 11 26
Directions
Adults - Take 1 easy to swallow tablet twice daily with meals or as professionally prescribed Children under 12 years - Only as professionally prescribed. If symptoms persist, see your healthcare professional
Storage information
White, vanilla flavoured tablet with easy to swallow coating. Store below 30C. Protect from moisture

Source: TGA website
(<http://www.tga.gov.au/pdf/consult/consult-labelling-packaging-review-120524.pdf>)

16. From the 3 examples shown above, which one do you prefer, as “key-information section”?

- Example A
- Example B
- Example C

a. Could you please briefly explain your answer?

17. Thinking of the Key Information **example you preferred**, please rate on the following topics:

	Very low quality								Very high quality	
	1	2	3	4	5	6	7	8	9	
General design of the “key information section”	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Overall quality of the information	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Ease of understanding the message (content)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Impact on patients’ adherence to treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Overall value to patients in general	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Overall value to elderly patients	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Overall value to patients with low literacy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Overall quality of the “key information section”	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	

18. What aspect(s) do you dislike most on the other two examples? (open question)