

Readability and comprehensibility of package leaflets

- recent efforts for improvement within the EU
and a historical review

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List of Abbreviations

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices)
AG	Arbeitsgemeinschaft (working group)
AMG	Arzneimittelgesetz (German Medicinal Products Act)
ARTL	Always Read the Leaflet – Getting the best information with every medicine
BBW	Black Box Warning
BEUC	The European Consumer Organisation
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)
BPG-PL	Best practice guidance on patient information leaflets
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CMS	Concerned Member State
CP	Centralised procedure
DAISY	Digital Accessible Information System
DBSV	Deutscher Blinden- und Sehbehindertenverband (German Blind and Visually Impaired Association)
DCP	Decentralised procedure
DRIVER	Digital Repository Infrastructure Vision for European Research
EC	European Commission
EEA	European Economic Area
EHIS	European health interview survey
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPF	European Patients` Forum
ePI	electronic product information
ePL	electronic package leaflet
EU	European Union
FDA	Food and Drug Administration
HCP	Health care professional
HMA	Heads of Medicines Agencies
MA	Marketing authorisation

MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual recognition procedure
MS	Member State (of the European Union)
NCA	National competent authority
NIVEL	Netherlands institute for health services research
NOMA	Norwegian Medicines Agency (Statens legemiddelverk)
NTA	Notice to Applicants
OTC	Over-the-counter
PDF	Portable Document Format
PEI	Paul-Ehrlich-Institute
PI	Product information
PIL	Package information leaflet
PIL-S study	Study on the Package Leaflets and the Summaries of Product Characteristics of Medicinal Products for Human use
PILS-BOX study	Feasibility and value of a possible “key information section” in patient information leaflets and summaries of product characteristics of medicinal products for human use
PL	Package leaflet
pt.	Points, used for measuring font size, 1 point = 0.3528 mm
QR code	Quick Response code
QRD	Quality Review of Documents
RMS	Reference member state
SmPC	Summary of product characteristics
SWOT	Strength, Weakness, Opportunity and Threat
TGA	Therapeutic Goods Administration – a division of the Australian Government Department of Health and Ageing
UK	United Kingdom
USA	United States of America
WADA	World Anti-Doping Agency
XML	eXtensible Markup Language

1 Introduction

In the European Union (EU), a medicinal product may only be placed on the market if it is authorised by a competent authority, either the European Commission (EC) or the competent authority of a single Member State (MS). An authorisation granted by the EC under the centralised procedure (CP) is automatically valid in all MSs. Both the decentralised procedure (DCP) and mutual recognition procedure (MRP) lead to an authorisation in at least two MSs, the reference Member State (RMS) and the concerned Member State (CMS). A purely national authorisation procedure leads to an authorisation in a single MS.

In order to obtain a marketing authorisation (MA) for a medicinal product, the application must contain, among other documents, a product information (PI) which is authorised by the competent authority [1]. The PI consists of the summary of product characteristics (SmPC), the package leaflet (PL) and the labelling, i.e. the information on the immediate and outer packaging [2]. Once the PI has been authorised, it may be amended only with the approval of the competent authority.

The SmPC is the final description of the medicinal product describing its qualitative and quantitative composition, pharmacodynamic and pharmacokinetic properties, contraindications, interactions with other medicinal products as well as adverse reactions. Furthermore, it provides guidance on the use of the medicinal product in its therapeutic indication. The SmPC serves as a source of information mainly for health care professionals (HCPs) such as doctors and pharmacists. They can either obtain the information directly from the SmPC or access databases of various software solutions that have integrated the information contained in the SmPC [1,3].

1.1 Purpose of the package leaflet

The PL, also known as package insert or package information leaflet (PIL), informs the patient about the purpose and the correct use of the medicinal product. The PL is prepared in accordance with the SmPC and contains information that should be known prior to the use of the medicinal product such as contraindications, warnings and interactions as well as information on possible side effects. Since the PL must be included in each package, unless all the required information is stated on the labelling, it is the ideal means of informing the patient how to use the medicinal product appropriately and safely. In order to fulfil this purpose, it is

obvious that the PL must be readable and comprehensible to the general public. Law also requires this but there is constant criticism that the PL is difficult to understand and the right information is difficult to find. The PL can only fulfil its purpose if the information it contains is read, understood, believed and remembered. Failure to achieve this goal may result in medication errors that cause side effects or non-adherence to medication due to misinterpretation of the risk of side effects. Vulnerable groups such as the elderly or those with a low level of education appear to be particularly affected [1,3]. Hence, it is interesting to know which groups of patients take the most medicines.

The European health interview survey (EHIS), carried out between 2013 and 2015, examined the self-reported use of medicines by people aged 15 and over in all MSs. Respondents to the survey were asked whether they had taken medicines in the last two weeks. The survey found that in almost all MSs the use of prescription medicines was lowest (21.9%) in the age group of 15-24, increased with age and was highest (87.1%) in the oldest age group of 75 years and older. In addition, the use of prescription medicines was higher among women and people who had completed no more than lower secondary education. The use of over-the-counter (OTC) medicines was highest among 25-34 year olds (37.0%) and 35-44 year olds (37.1%) and among people with higher education [4].

1.2 Legal framework

1.2.1 Directive 2001/83/EC and Regulation (EC) No 726/2004

Directive 2001/83/EC [5] applies to medicinal products authorised via DCP, MRP or a national authorisation procedure while Regulation (EC) No 726/2004 [6] applies to medicinal products authorised via CP. According to Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) No 726/2004 a marketing authorisation application (MAA) for a medicinal product has to be accompanied by several particulars and documents including the SmPC and PL [5,6]. Thus, both are crucial documents for granting a MA, whereas it is irrelevant whether the authorisation is obtained through decentralised or centralised procedure [1].

Article 11 of Directive 2001/83/EC describes the information and its order, which must be included in the SmPC. For details, refer to *Annex 7.1*. Title V of Directive 2001/83/EC deals with the labelling and PL. Pursuant to Article 9(4) of Regulation (EC) No 726/2004, the SmPC and PL of a centrally authorised medicinal product must comply with Article 11 and Title V of Directive 2001/83/EC respectively [5,6]. Article 59(1) of Directive 2001/83/EC states that the PL must be prepared in accordance with the SmPC and also describes the information and its

order which must appear in the PL. For details, refer to *Annex 7.2*. Pursuant to Article 58 of the same Directive, the PL has to be included in the packaging of all medicinal products unless all required information is directly conveyed on the immediate or outer packaging. Directive 2001/83/EC also addresses the comprehensibility of the PL through several Articles [5], which are described in detail in *Section 2.1.1*.

1.2.2 Guidelines and Templates

Three guidelines provide detailed information on the correct implementation of the above legal requirements. These guidelines influence the PL directly or indirectly, and are as follows:

- The Guideline on Summary of Product Characteristics (SmPC), September 2009 [7], hereinafter referred as the “SmPC Guideline”;
- The Guideline on the readability of the labelling and package leaflet of medicinal products for human use, Revision 1, 12 January 2009 [8], hereinafter referred as the “Readability Guideline”;
- The Guideline on the packaging information of medicinal products for human use authorised by the Union, July 2018 [9], hereinafter referred as the “Packaging Information Guideline”.

The SmPC Guideline indicates that the SmPC is an intrinsic and internal part of the MA. The content of the SmPC is agreed with the competent authority during the authorisation procedure and must not be modified unless the amendment is approved by the competent authority. The Guideline defines the content in each section of the SmPC and sets out some principles for presentation of information including the recommendation to use clear and concise language. Since the PL has to be drawn up in accordance to the SmPC, it is also affected by this recommendation [7].

The currently valid Readability Guideline was published in January 2009 and became effective in June of the same year. It refers to various articles of Directive 2001/83/EC, which state that the PL and labelling must be legible and comprehensible. The Readability Guideline indicates that its main purpose is to ensure that the information on the labelling and PL is understood by patients so that they can use their medicines appropriately and safely. It is intended to assist the marketing authorisation holder (MAH) in presenting the information required by Title V of Directive 2001/83/EC and gives advice on the design and layout in order to improve the quality of the information. The guideline is divided into three chapters, with Chapter 1 dealing with the readability of the PL and labelling. It includes recommendations for font and font size, design

and layout, the use of headings and print colour as well as syntax, writing style and paper quality. In addition, the Readability Guideline recommends the use of QRD templates, which are explained below. Chapter 2 describes how the PL can be made available in formats suitable for blind and visually impaired patients. Finally, Chapter 3 provides guidance on how to carry out user consultation with target patient groups required by Article 59(3) of Directive 2001/83/EC and its Annex includes an example of a method for a user testing [8].

The Packaging Information Guideline describes how the provisions of Directive 2001/83/EC apply in the case of an authorisation to be granted by the EC. Pursuant to Article 9(4) of Regulation (EC) No 726/2004, the SmPC and PL of a medicinal product authorised by the EC must comply with the requirements of Article 11 and Title V of Directive 2001/83/EC respectively. The Packaging Information Guideline states that the PL of a centrally authorised medicinal product should be the same in all MSs. It must be written in the language or languages of the MSs in which it is placed on the market. If more than one language has to be used, the content of all language versions must be identical and the overall readability of the PL must not be compromised. The Packaging Information Guideline also mentions various articles of Directive 2001/83/EC stating that the PL must be clear and comprehensible and refers to the Readability Guideline as well as the QRD templates. In addition, according to the Packaging Information Guideline the PL should indicate that suitable formats are available for the blind or visually impaired. Finally, the guideline states that the PL and labelling are linguistically checked during the marketing authorisation procedure and that the European Medicines Agency (EMA) reviews mock-ups* and specimens* for legibility to contribute to the safe use of medicines [9].

As mentioned in the Readability Guideline and the Packaging Information Guideline, practical guidance is provided by the QRD templates to ensure that all information required by Directive 2001/83/EC is included in the correct order in the SmPC, PL and labelling. Using QRD templates leads to consistency between different medicinal products of all MSs. QRD templates provide standard headings and statements that must be used by the MAH whenever they are applicable [3,10].

* A specimen is a sample of the actually printed outer and immediate packaging and the PL, i.e. the sales presentation. A mock-up is a copy of the design of the flat artwork in full colour. After cutting and folding where necessary, the three-dimensional representation of the labelling text becomes clear. It is usually printed on paper and not on the material of the sales presentation [8].

1.3 Aim of the thesis

This thesis is intended to examine and summarise the efforts that have been made within the EU to ensure the readability and comprehensibility of the PL. In this context, the changes that have been made to laws, guidelines and templates so far will be dealt with. Furthermore, the latest efforts within the EU will be discussed. The questions that arise are in particular:

- What has been legally regulated in the EU so far and do these requirements lead to a sufficient comprehensibility of the PL?
- What efforts have been made recently in the EU?
- What have individual MSs done? Do individual MS face particular difficulties? Do some of them have a leading role?
- What has been done for specific patient groups, e.g. blind or visually impaired patients, older people and those with poor reading skills?
- Are there new communication channels or formats that could increase the comprehensibility of PLs? Is an electronic package leaflet (ePL) an option?
- Is it possible to solve frequent points of criticism?

2 Results

2.1 Historical review

This chapter describes the efforts within the EU to ensure and improve the readability and comprehensibility of PLs from 2001 to 2014 with the exception of *Section 2.1.3* which describes the development of the QRD templates to date.

2.1.1 Amendments to Directive 2001/83/EC affecting the package leaflet

As mentioned in *Section 1.2.1*, Directive 2001/83/EC addresses the comprehensibility of the PL and SmPC through several Articles. These have been incorporated into the Directive over time. In the following, the amendments to Directive 2001/83/EC concerning the SmPC and PL are described. Where appropriate, the relevant amendments have also been made to Regulation (EC) No 726/2004, but as the Regulation often refers to the Directive, the amendments are only described in relation to Directive 2001/83/EC [5,6].

After taking effect in December 2001, Directive 2001/83/EC was amended several times with a substantial amendment regarding the SmPC and PL in 2004 [1]. Directive 2004/27/EC [11] replaced Articles 11 and 59 of Directive 2001/83/EC which describe the necessary information in the SmPC and PL respectively. This replacement has changed the order in which individual information has to appear in the PL. Less important information, such as information on excipients, available package sizes and information on the MAH and manufacturer, has been moved to the end of the PL. This made more important information such as contraindications, warnings and precautions more visible at the beginning of the PL. In addition, a sentence has been included in the PL explicitly stating that the patient should contact the doctor or pharmacist with any questions concerning the use of the medicinal product. It is also important to note that the amendment in 2004 has made user consultation with target patient groups mandatory through the introduction of Article 59(3). The article points out that the necessary legibility and comprehensibility of the PL should be checked and ensured through user consultation. Since then, Article 61(1) requires that an assessment of the consultations be submitted to the competent authority in a MAA [1,11]. Article 56 requires that the labelling and PL are “easily legible, clearly comprehensible and indelible” [5]. In 2004, Article 56a was implemented which requires the provision of the PL in formats suitable for blind and visually impaired people on request from patient organisations [11]. As per Article 62, symbols or pictograms may be

included in the PL if they clarify information mentioned in Article 59(1). The PL may also contain other information if it is compatible with the SmPC, useful to the patient and not used to advertise the medicinal product [5]. The statement in Article 63(2) of 2001 that “the package leaflet must be written in clear and understandable terms for the users” [12] has been specified in 2004 by emphasizing that the design also contributes to comprehensibility. Hence, the PL must “be written and **designed**” [11] in such a way as “to be clear and understandable” [11] and to enable the patient “to act appropriately, when necessary with the help of health professionals” [11]. The PL must be written in the official language or languages of the MSs in which the medicinal product is placed on the market. As a result, in MSs that have more than one official language, medicines have multilingual PLs [5]. Furthermore, Article 65, which in 2001 still pointed out that the EC should publish “**as necessary*** [...] guidelines” [12], i.a. on the legibility of the labelling and the PL, has been strengthened in 2004 so that the EC should in any case “draw up and publish **detailed*** guidance [...] in consultation with the Member States and the parties concerned” [11]. The guidance shall include the wording of specific warnings for certain categories of medicinal products, the legibility of the information on the labelling and in the PL and the way in which excipients must be indicated on the labelling [5]. In December 2008, it was proposed to include a key information section in the SmPC and PL. This new section should allow HCPs and patients to quickly identify important safety messages that are balanced with information on the benefits of medicines [13]. However, this proposal was not included in Directive 2001/83/EC as it was amended in by Directive 2010/84/EU [14]. The EC first wanted an evaluation of current evidence on the added value of such a section [13]. For details, refer to *Section 2.2.2*.

The amendment of Directive 2001/83/EC in 2010 mainly aimed to extend and improve pharmacovigilance activities in the EU and included some changes that had an impact on the PL and SmPC. In Articles 11 and 59(1) a passage has been added stating that HCPs or patients should be required by the SmPC or PL to report any suspected adverse reaction to the competent authority of the MS where the product is placed on the market [14]. This is not directly related to the comprehensibility of PLs but should nevertheless be mentioned, as it is intended to increase the safe use of medicinal products, as does improved readability. The fact that, in Article 59(1)e, the sentence from the 2001 version that “the patient should be expressly invited to communicate any undesirable effect which is **not mentioned*** in the leaflet to his doctor or to his pharmacist” [12] was deleted in 2010 [14], should also lead to a safer use of medicinal

* Note: The words in the official legal text are not printed in bold type but were highlighted in the quotation in order to clarify the differences.

products and can be seen as a positive influence on the comprehensibility of the PL. Thus, the patient is no longer left “alone” with the evaluation of side effects. In addition, Article 59(4) was incorporated into Directive 2001/83/EC by the amendment in 2010 to assign the EC to submit an assessment report to the European Parliament and the Council by 1 January 2013. This assessment report should describe the current shortcomings of the PL and SmPC and propose how these shortcomings can be improved to better meet the needs of the patients and HCPs [1,14]. For details, refer to *Section 2.2.1*.

Finally, Article 63 of Directive 2001/83/EC was amended by Directive 2012/26/EU [15]. Article 63(3) of 2001 defined that for certain medicinal products which are not supplied directly to the patient, the competent authorities, may allow that not all the required particulars appear on the labelling or that the PL is not printed in the official language of the MS. This Article was reworded in 2012 to provide that such an exemption may also be granted in the event of serious problems with the availability of the medicinal product and that the competent authorities may take such measures, as they deem necessary to protect human health [12, 15].

2.1.2 The Readability Guideline

The Readability Guideline was first published in September 1998 and stated that its main purpose was to ensure that the label and PL were readable. Applicants for a MA when preparing the specimens or mock-ups of the sales presentation and the PL should follow the guidance provided [16]. As per Article 8 of the then valid Council Directive 92/27/EEC the PL “must be written in clear and understandable terms for the patient and be clearly legible” [17]. Annex 1a of the Readability Guideline contained an example of a model leaflet and Annex 1b provided further information on the content of that model leaflet. Finally, Annex 2 contained an example of a method for testing the readability of the PL based on an approach by David Sless and Rob Wiseman from the Communication Institute of Australia [16]. Thus, as early as 1998, MAHs were advised to test the readability of the PL with target patient groups, whereas this user consultation was not yet mandatory at that time.

Council Directive 92/27/EEC was repealed by Directive 2001/83/EC in 2001 [5]. In addition, Directive 2004/27/EC led to several amendments of Directive 2001/83/EC, including the introduction of legal obligation for user consultation [11]. Hence, the first revision of the Readability Guideline became necessary and was published in 2009. A comparison of the 1998 and 2009 guidelines reveals the following differences:

In the 2009 version, a larger font size of 9 points (pt.) measured in Times New Roman is recommended. Previously, a font size of at least 8 pt. in Didot was sufficient. The recommended

space between the lines of at least 3 mm remains unchanged. Moreover, in the 2009 version a larger font size should be considered when the medicinal product is intended for patients with visual impairment. It is also recommended to use a font in which similar letters and numbers, such as “i”, “l” and “1” can be easily differentiated. In addition, neither italics nor underlining should be used as this may affect legibility, while italics may be used for Latin terms. Capitals should only be used for emphasis [8,16].

The first revision of the Readability Guideline also contains guidance on design and layout such as not using justified text, i.e. text aligned to both the left and right margins. A column format that is known from newspapers is recommended as it may help the reader to find his way through the information. Furthermore, sufficient line spacing and contrast between text and background should be maintained. In multilingual PLs, a clear demarcation between the different languages should be ensured [8].

According to the 2009 version, the importance of headings should be emphasised, e.g. by bold type and different colours. As in the previous version, the revised version still points out that no more than two levels of headings should be used, as otherwise the reader cannot easily orientate himself in the text. Regarding the notes on print colour, the 2009 version adds that dark text should be used on a light background, but a reverse type (light text on a dark background) can be used to highlight information, e.g. certain warnings [8,16].

Regarding syntax, the revised version emphasizes that people with poor reading skills and poor health literacy should be considered. Simple words with few syllables should be used and long sentences should be avoided. However, the definition of a “long sentence” as a sentence of more than 20 words was removed in the revision of 2009. In addition, the new version recommends not using more than five or six bullet points. In the previous version, no more than nine bullet points were recommended if the context was simple or five if the context was complex [8,16].

Concerning the paper to be used, the revised guideline no longer recommends a specific basis weight but a sufficiently thick, non-glossy paper to avoid transparency and light reflection. Therefore, uncoated paper should be used [8,16].

In addition, the newer version of the Readability Guideline also contains more detailed information on the writing style to be used and on the use of symbols and pictograms. It is also recommended to use the QRD templates for the first time. Thus, the model leaflet of the first version could be removed [8,16].

As described in *Section 2.1.1*, the amendment of Directive 2001/83/EC in 2004 also led to the inclusion of Article 56a [11]. Chapter 2 of the first revision of the Readability Guideline

therefore contains specific recommendations on how to address the concerns of blind and partially sighted patients. According to the Readability Guideline, the provision of Article 56a applies to medicinal products authorised after 30 October 2005 and not immediately to products authorised before that date. Nevertheless, the MAHs are recommended to apply the provision to all medicinal products as soon as possible. Some advice is given on what to consider when indicating the name of the medicinal product in Braille. The text under Braille dots must remain easily legible and multilingual packages must contain the product name in Braille in all concerned languages. The revised Readability Guideline also provides some examples to meet the requirement that PLs have to be provided in special formats suitable for blind and partially sighted patients. In order to create a suitable print for partially sighted patients it is suggested that sans serif typefaces in a font size of 16-20 pt should be used. Moreover, an adequate contrast (black letters on white paper), word spacing, text alignment, line spacing, layout and paper quality should be ensured. For the blind, hearing formats (CD-ROM, audiocassette, etc.) and in certain cases PLs in Braille format may be used. The MAH should also take into account recommendations from representatives of blind organisations [8].

Finally, Chapter 3 of the revised Readability Guideline provides guidance concerning the consultations with target patient groups. It is pointed out that the requirement for user consultation applies to all MAs granted after 30 October 2005. For existing MAs, user consultations only need to be performed if significant changes are made to the PL by a variation. Furthermore, it is described that Directive 2001/83/EC does not specify exactly how the requirement for user consultation can be met. One way of fulfilling the requirement in Article 59(3) is to carry out a so called “user testing” in which the readability of a specimen is assessed by a group of selected test subjects. However, the authorities on a case-by-case basis can also accept alternative test methods. In this case, the MAH has to prove that the alternative test method leads to meaningful results. It is also emphasized that compliance with QRD templates does not mean that the MAH does not have to perform user testing or any other form of user consultation. In addition, it is described in which cases user consultation must always be carried out, e.g. for a new active substance, a change in the legal status (switch from prescription to non-prescription status) or medicinal products with critical safety issues. Cases are also described in which the MAH does not have to conduct a user consultation and can instead refer to a similar PL that has already been approved. In this context, the Readability Guideline refers to the CMD(h) advice “Consultation with Target Patient Groups – meeting the requirements of Article 59(3) without the need for a full test – Recommendations for Bridging” [8]. This recommendation has been last updated in December 2017 [18]. In addition,

Chapter 3 states that it is sufficient to test the PL in **one** language of the European Economic Area (EEA). In the context of the CP, DCP and MRP the English version of the PL is examined. The MAH, in consultation with the national competent authority (NCA) or EMA, is responsible for ensuring that the PL is "faithfully" translated into the individual languages of the MSs. Chapter 3 also stipulates that the results of user consultation should be presented in Module 1.3.4 of the MAA and explains to what the competent authority should pay attention when evaluating the results. Finally, the Annex to the Readability Guideline describes an example of how user testing can be performed, what needs to be considered when recruiting participants and where participants can be acquired. A test is considered successful if 90% of the participants are able to find the information they are being asked for and 90% can show that they understand the information [8].

The main recommendations of the two Readability Guidelines are listed in Table 1 on the following page.

	Readability Guideline 1998	Readability Guideline 2009
Type size and font	8 points Didot; space between lines at least 3 mm; avoid words in full capitals, but capitals may be useful for emphasis;	9 points Times New Roman; space between lines at least 3 mm; “i”, “1” and “l” shall be easily distinguishable; no use of italics or underlining, but italics are allowed for Latin terms; avoid widespread use of capitals, but capitals may be useful for emphasis;
Design and layout of the information	n.a.	no “justified” text; space between one line and the next = 1.5 x space between words on a line; no background images; column format for the text; multilingual leaflets: clear demarcation between languages;
Headings	different type, different colour	bold type face, different colour
Print colour	use of several colours possible; colours must be clearly distinguished from background; reserve red colour for very important warnings;	dark text on light background; reverse type to highlight information;
Syntax	avoid long sentences (sentence with more than 20 words); no more than 70 characters in one line; avoid subordinate clauses; no more than 9 items where bullet points are simple, no more than 5 items where they are complex;	consider people with poor reading skills; use simple words of few syllables; avoid long sentences; use a couple of sentences rather than one long sentence; no more than 5 or 6 bullet points in a list;
Style	active style; give instructions, followed by explanations; reasons should be given for recommended measures;	active style; give instructions, followed by reasonings; no abbreviations or acronyms; translate medical terms, place medical term directly after lay term;
Paper	long leaflets: paper size A4/A5; paper weight: at least 40g/m ² ;	sufficiently thick; non-glossy, uncoated;
Use of symbols and pictograms	may be used as additional measure if they clarify the message;	may be used to clarify or highlight certain aspects of the text; should not replace the text;
Template	model leaflet in Annex 1a	reference to QRD templates

Table 1: Recommendations of the 1998 and 2009 Readability Guidelines [8,16].

2.1.3 QRD templates

In 1996, the EMA established a Working Group on Quality Review of Documents (QRD). The working group consists of two experts per MS, selected by the NCAs, and is complemented by one representative each from the EC, the Translation Centre for the Bodies of the EU as well as the secretariat of the Agency. The tasks of the working group include enhancing legibility, linguistic clarity and consistency of the PI [19,20].

QRD templates for PI are provided in 24 languages on the EMA website, i.e. in all official EU languages as well as Icelandic and Norwegian. Although the QRD template is only a guidance document and thus not legally binding, its use ensures that patients find the same standardised headings and statements in the same order in all PLs of the European MSs, Norway, Iceland and Liechtenstein. This ensures consistency between the PLs of different medicinal products in different countries of the European Economic Area (EEA).

The QRD template is available for centrally and nationally authorised medicinal products. The QRD template for CP was first released in 1997 and has been updated regularly since then, with the latest version 10.1 released on 28 June 2019. The amendments to Directive 2001/83/EC described in *Section 2.1.1* and the revision of the Readability Guideline described in *Section 2.1.2* led to changes in the QRD templates. In addition, since QRD template version 7.0, an annotated version of the English QRD template for CP is available on the EMA website. The annotated version contains further advice and explanations for the applicant. The QRD template for nationally authorised medicinal products from the mutual recognition or decentralised procedure was first published on the EMA website in 2011 and was last updated on 9 February 2016 with version 4.0 [10,21,22]. An annotated version of the QRD template for MRP/DCP, which is based on the one for CP is available on the website of the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) [23]. The QRD template for MRP/DCP differs only slightly from the one for CP, e.g. local representatives of the MAHs and further information are missing at the end of the PL [3,22,23].

In the following, the annotated QRD template for PLs of the CP is described. The text displayed in the annotated QRD template is printed in three different colours. The standard headings and statements to be used by the MAH are displayed in black while explanations and notes are displayed in green. Orange text refers to the corresponding section or information of the SmPC to be displayed in a patient-friendly manner in this specific section of the PL. Various brackets, such as “{text}” and “<text>” [3], indicate whether information should be filled in or text

should be selected or deleted, depending on whether or not it applies to the medicinal product in question [3].

Particularly interesting is the green printed text. It says that by following the order indicated and the wording of the headings and statements, it is ensured that the PL contains the information required by Title V of Directive 2001/83/EC. However, the annotated QRD template indicates that the layout of the PL presented in the template is intended only for the Word/PDF document to be submitted to the competent authority in an application. The formatting (in particular font and text size) must not be transferred to the printed material; instead, reference is made to the guidance provided in the Readability Guideline, as design and layout are key elements for the readability of the final printed PL [3].

Since version 3 of the QRD template, there has been an information box at the beginning of the PL, which distinguishes between prescription and OTC medicines, and a list of contents [22]. In section “1. What X is and what it is used for” [3], it is pointed out that, in addition to the indication, the age group for which the medicinal product is intended should be indicated.

Since QRD template version 8 benefits of the medicine can be listed under the heading “How X works” [3] on a case-by-case basis if they are compatible with the SmPC and not promotional. Moreover, it is shown what content such a benefit section could have. In addition, QRD template version 8 was the first one reflecting the experience of five years of user testing and feedback from several stakeholders such as patient and consumer groups, NCAs, the pharmaceutical industry and academia. The EMA itself saw the revision in 2011 as an improvement in the comprehensibility of PLs [3,22,24].

It is stated that user testing has shown that patients have most problems in understanding the information in section “2. What you need to know before you <take> <use> X” [3], because of the size of this section. Nevertheless, complex details must not be omitted. Hence, it is important to include additional sub-headings with a clear hierarchy to help patients to orientate themselves and to list all contraindications, warnings and precautions. The order should be based on severity and patients should receive clear instructions as to what they should do to minimise the potential risk.

In section “3. How to <take> <use> X” [3] it should not only be explained how the medicine is used correctly but also what can happen if the patient does not adhere to it. User testing has shown that such details increase understanding, e.g. “Do not break or crush the tablet(s). If you do, there is a danger you could overdose because this medicine will be absorbed into your body too quickly” [3]. The opening of containers that are difficult to open, e.g. child-resistant containers, should be described with the aid of illustrations.

In section “4. Possible side effects” [3] it is pointed out that this section should be divided into two sections. Firstly, the most serious side effects should be mentioned, and the patient should receive clear instructions as to what action to take and how quickly. Secondly, all other side effects should be listed in descending order of frequency.

The frequency of side effects should be described in words and relating numerical data:

“Very common:	may affect more than 1 in 10 people
Common:	may affect up to 1 in 10 people
Uncommon:	may affect up to 1 in 100 people
Rare:	may affect up to 1 in 1,000 people
Very rare:	may affect up to 1 in 10,000 people
Not known:	frequency cannot be estimated from the available data” [3]

This frequency convention was implemented as green text in version 8 of the annotated QRD template in 2011. The explanation in the QRD template also mentions that the frequency convention should no longer appear before the list of side effects as it takes up space and user testing has shown that this is misleading for the patient [3,22]. It is noticeable that this frequency convention differs from the one contained in the Readability Guideline from 1998 and the reworded version published by the EMA in 2007. Previously, the explanation with numerical data was double sided, such as “common > 1% and < 10%, (less than 1 per 10 but more than 1 per 100)” [16] in the Readability Guideline from 1998 and “common: affects 1 to 10 users in 100” [25] published by the EMA in 2007. According to the annotated QRD template the frequency convention has been changed to the one-sided explanation as user testing has shown that double-sided expressions are not well understood [3]. However, chapter 4.8. of the SmPC must state the frequency of side effects according to the MedDRA frequency convention [3], which continues to use double-sided expressions. In the latest version 21.0 of the MedDRA frequency convention, the frequency information shall be provided as follows:

“Very common	($\geq 1/10$)
Common	($\geq 1/100$ to $< 1/10$)
Uncommon	($\geq 1/1,000$ to $< 1/100$)
Rare	($\geq 1/10,000$ to $< 1/1,000$)
Very rare	($< 1/10,000$)
not known	(cannot be estimated from the available data)” [26]

Hence, the information displayed in the PL is not completely in line with the information in the SmPC, which is required by Article 59(1) of Directive 2001/83/EC [22].

Additionally, in contrast to the SmPC, the side effects in the PL should not be listed according to system organ classes, as this is not understandable for the patient. However, in PLs of older

medicinal products where the frequency of side effects is often unknown, patient-friendly terms for body parts can be used as headings such as “skin, stomach and gut” [3].

In section “6. Contents of the pack and other information” [3], it is noted that the inclusion of local representatives in the product information annexes published on the EMA website is not required but optional. If the list of local representatives has been included in the product information annexes, it is sufficient to name the local representative concerned in the printed PL.

Finally, under the heading “Other sources of information” [3], a large font should be used to indicate how visually impaired patients can access the information in alternative formats such as Braille, audio, CD-ROM or large print. In addition, for medicines mainly used in hospitals, a tear-off section may include relevant practical information about preparation, handling and incompatibilities, posology, overdose or monitoring and laboratory tests under the heading “The following information is intended for healthcare professionals only” [3,22].

2.1.4 Consultation with target patient groups

Consultations with target patient groups should ensure that the PL is easy to use, clear and comprehensible. Although user consultation does not directly improve the legibility of the PL, it can reveal weaknesses and thus trigger an improvement. Guidance on how to conduct these consultations can be found in Chapter 3 of the current Readability Guideline as described in *Section 2.1.2*. Either user testing can be carried out, for which an example is given in the Annex of the Readability Guideline, or another test method can be used if justified by the applicant [1,5,8]. The CMDh has published the guidance “Consultation with target patient groups - meeting the requirements of Article 59(3) without the need for a full test - recommendations for bridging” and the “Position paper on user testing of package leaflets”, which was last updated in December 2016. The guidance “Recommendations for bridging” clarifies when the competent authorities consider two PLs to be sufficiently similar in terms of content and layout. The “daughter” PLs should have the same design, layout and writing style as the “parent” PL for the bridging to succeed. The position paper describes two methods of user testing. First, the “Australian” method which is also described in the Readability Guideline and in which the questions are asked orally, and a self-completion method in which the respondents answer the questions in writing. The latter test method is more realistic as the patient usually reads the leaflet at home by himself. The disadvantage, however, is that the test subject must not only be able to read but also write in order to take the test. Therefore, certain test subjects are partly excluded. In its position paper, however, the CMDh recommends that

self-completion should be accepted as a method for user testing in accordance with Article 59(3) of Directive 2001/83/EC [18,27].

However, in most MSs user consultation is only required for authorisations granted after 30 October 2005. Only where a PL is substantially modified by a variation or a procedure pursuant to Article 61(3) of Directive 2001/83/EC is a user consultation also required for existing authorisations granted before 30 October 2005. Finally, it should be noted that experience gained from user consultation is important as it may influence the development of guidance documents such as the QRD templates as described in *Section 2.1.3* [1,8,24].

2.2 Recent efforts within the European Union

2.2.1 The PIL-S study

As described in *Section 2.1.1*, the EC was requested by Directive 2010/84/EU to submit an assessment report on the readability of the SmPC and PL and their benefits for HCPs and patients to the European Parliament and the Council. For this report, the EC should cooperate with the EMA and NCAs and consult patient organisations, consumers, doctors and pharmacists, social health insurers and other interested parties [14]. The “Study on the Package Leaflets and the Summaries of Product Characteristics of Medicinal Products for Human use” (PIL-S study) [1] was carried out by the Netherlands institute for health services research (NIVEL) and the University of Leeds. The study was published in July 2014 and addresses three objectives:

- identification of possible shortcomings and positive points of the PL and SmPC as a source of information on prescription and non-prescription medicines for patients and HCPs;
- an assessment of the causes of identified shortcomings and their potential consequences for the health of patients;
- recommendations for improvement of the PL and SmPC based on this assessment.

It is therefore structured in three corresponding work packages. The evaluation was based on a literature search, a European wide stakeholder survey and an online discussion forum with experts [1].

The literature search was carried out in several databases such as PubMed and Embase and led to 61 articles in international journals that met all inclusion criteria. It was examined what is already known in the literature about positive aspects and possible problems with the PL and SmPC in terms of content, design and layout. According to the authors of the PIL-S study, the

literature search showed that the comprehensibility of PLs has to be improved. The studies examined showed that information on interactions and contraindications is too complex and difficult to understand and that dosage instructions are too inaccurate. It should be noted that the deficiencies were mainly found in PLs prepared before 2005, i.e. before the introduction of user consultation. A study also investigated the effect of user testing based on German PLs and found that it increases the comprehensibility. However, it was also found that patients do not necessarily benefit from user consultation, as in most MSs including Germany, it is only mandatory for newly authorised medicinal products. In the UK, on the other hand, the PLs of existing medicinal products need to be tested as well [1]. For further information, refer to *Section 2.3.2*.

Some studies also described that a benefit section should be introduced into the PL to provide patients with more comprehensive information about the medicine. In addition, some studies explained that patients often overestimate the risks of medicinal products, especially when verbal descriptors such as “rare” or “common” are used alone without explaining them in quantitative percentages [1].

20 studies investigated the design, layout and structure of PLs and found that a larger font size (up to 12 pt. Times Roman), larger paper format for more readable text and illustrations should be used. A lower reading level (below 5th or 6th grade) and shorter PLs should be achieved. Two studies proposed a new structure for the PL. Other studies showed that the use of pictograms in PL leads to higher comprehensibility, especially in low literate patients [1].

In the European wide stakeholder survey patient and consumer organisations, HCPs, pharmaceutical companies, regulatory officers and user testing companies were consulted twice through an online structured questionnaire, with the second questionnaire aiming at clarifying unclear aspects and gaining a deeper understanding in some topics participants mentioned in the first questionnaire. The participants came from all over the EU with an overrepresentation for the UK, Germany, Croatia, and the Netherlands [1].

In work package 1, participants were asked to rate three out of five original PLs sent to them in terms of content, layout and overall quality. The authors of the PIL-S study consulted the EMA with regard to the selection of the five PLs and ensured that a broad spectrum was covered. The selection of PLs included non-prescription and prescription medicines, medicinal products authorised before and after the introduction of user consultation and medicinal products authorised via the centralised or decentralised procedure. Four PLs were distributed in the format in which they were actually contained in the package. The layout varied considerably, from a long PL printed in black and white on thin paper to a full-coloured booklet printed on

glossy thick paper. One of the leaflets was deliberately sent in A4 format as a possible alternative as the font size was larger and the pictograms clear. A multilingual mock-up was also evaluated. According to the authors of the PIL-S study, the participants of the survey were not satisfied with the overall quality of the PLs. The full-coloured booklet received the highest ratings for content quality, layout and overall quality. This PL was issued after the introduction of user consultation in 2005 [1].

Participants were also asked whether they would prefer not to offer multilingual PLs in countries with more than one official language, but separate PLs in each language. Only 36.1% of patient organisations, 50% of HCPs and just 13.3% of representatives of the pharmaceutical industry were in favour of separate PLs in each language. Those in favour of separate PLs pointed out the fact that the information would be easier to find [1].

When they were asked whether the PLs contained sufficient information for specific target groups, the majority of HCPs complained that the PLs do not contain sufficient information for elderly and multimorbid patients. Stakeholders agreed that a section on benefits should be included in the PL as it could improve comprehensibility, would be important for assessing risk information and could improve compliance with the treatment [1].

In work package 2, the stakeholders were asked which problems they knew about the comprehensibility of the PL and which positive aspects they were aware of. According to the participants, the contents of the leaflet are too difficult to understand, e.g. too many medical terms are used, there is too much text to read and too many side effects are mentioned. Patients could give up reading the long text and be discouraged from taking the medicinal product by mentioning the many side effects. The lack of understanding of the information in the PL may lead to non-compliance with the treatment (both intentionally and unintentionally). Regarding the layout, the participants saw problems due to the small font size and length of the text. The participants assumed that not only older and low literate patients but also patients in general have problems understanding the leaflet. According to the authors of the PIL-S study, the positive points mentioned by the participants regarding the PL were wishes for improvement rather than actual positive points [1].

In work package 3, the participants were asked what improvements could be made to the comprehensibility of PLs. Suggestions for improving the content included the use of lay language, shorter and simpler sentences and less information. Suggestions for improvements to the layout included larger font size, better design, highlighting of important information and shorter PLs. Some representatives of patient organisations suggested that patients could be

trained to read PLs. Some pharmaceutical industry representatives suggested using alternatives to the paper-based PL, such as the electronic package leaflet (ePL) [1].

With regard to the suggestions for improvement from the literature search and the stakeholder survey, it is obvious that some suggestions cannot be combined. A larger font size and a larger line spacing cannot be implemented if the PL is to become shorter overall. The authors of the PIL-S study therefore asked the participants about their preference. They stated that it is more important to use a larger font size and larger line spacing than to make the PLs shorter. When the participants were asked whether all side effects should be mentioned or only serious and common side effects, the patient organizations tended to list all side effects whereas the HCPs were inconclusive [1].

In addition, the participants were asked whether they knew the QRD templates, how they would evaluate their content and structure and whether any content was missing. Another question was whether the QRD templates should continue to be as regulated as the one assessed. The majority of the representatives of patient organisations and the pharmaceutical industry were of the opinion that the QRD templates do not lack sections, but that no content should be excluded either. When asked which sections were most likely to be omitted, the list of representatives of the MAHs and the introductory paragraphs were most frequently mentioned. A section with information on the benefits of the medicine was most often mentioned as missing. Most Stakeholders were in favour of keeping the content and structure of the QRD templates as strongly regulated as the one assessed. However, the representatives of the pharmaceutical industry would have liked more flexibility in the content of the QRD template, as they believed that different information should be stressed for different medicinal products [1].

Both, the literature research and the stakeholder survey suggested possible improvements. In the last stage of the PIL-S study, the online discussion forum, the suggestions for improvement should be examined more closely. The authors of the PIL-S study wrote to 57 people, 20 of whom agreed to participate and 10 of whom were very committed. The participants of the online discussion forum agreed on following points. The authorities should provide best practice examples of well-designed and understandable PLs, to which the MAHs could refer. Not only the final PLs should be shown, but also the development process of a good PL. The guidelines that describe how to create a good PL need to be improved. Providing both benefit information and risk information would improve the quality of the information in PLs. Although almost all participants agreed that risk information should be shorter, there was disagreement on how to achieve this goal. It was also suggested that patients should be more involved in the development of the PL [1].

After the literature search, the stakeholder survey and the online discussion forum have been completed, the authors of the PIL-S study formulated six conclusions and resulting recommendations to the EC [1]. The recommendations can be found in *Annex 7.3*.

Firstly, the EC should focus more on improving the PL than on the SmPC, as HCPs currently consider the quality of SmPCs to be adequate. With PLs, the language is too complex and the design and layout is not sufficiently user-friendly. Although vulnerable groups (elderly and less educated patients) are disadvantaged, the problems identified affect all patients.

Secondly, the existing guidelines should be adapted to provide more accurate information, e.g. on font size and line spacing, and more principles for good information design. The QRD template should remove unimportant sections, such as information on all package sizes, to make room for improvements in content and layout. In addition, the EC should consider whether the QRD template should allow more flexibility with regard to the recommended information for different medicinal products. A guideline for translation should be developed which not only specifies the principle of faithful translation, but one that also ensures that the lay language is not lost in translation.

Thirdly, patients should be more involved in the development of PLs. For example, user testing could be made more iterative, and text changes to information that has already been user-tested should also be re-checked by user testing.

Fourthly, EMA or NCAs should provide examples of good, user tested PLs for pharmaceutical companies. Not only should the finished PL be provided, but the development process should also be described.

Fifthly, electronic formats could offer new opportunities in the future to improve the PL. The EU should start to develop a strategy on how to inform EU citizens through electronic formats. In addition, the possibility for using the PL as part of the care process instead of a stand-alone source of information should be investigated.

Finally, electronic formats could be used in particular for multilingual PLs. The most important information could be contained in the paper version and further information in the electronic version. The EC should therefore include countries with more than one official language in the electronic media strategy [1].

2.2.2 The PILS-BOX study

As described in *Section 2.1.1*, in December 2008 there was a proposal to include a key information section containing important safety messages balanced with benefit information, as a new section, in the SmPC and PL [13]. However, this proposal was not included in

Directive 2001/83/EC as it was amended by Directive 2010/84/EU [13,14]. Before a key information section should be made mandatory, the EC requested a study on the added value of such a section. The study “Feasibility and value of a possible “key information section” in patient information leaflets and summaries of product characteristics of medicinal products for human use” (PILS-BOX study) [13] was published in July 2014 and intended to provide the EC with an assessment of the current evidence with regard to:

- the potential impact of introducing a key information section in the PL and SmPC in order to quickly identify important safety messages balanced with information on the benefits of medicinal products;
- the feasibility of adding a key information section in the context of the EU legislation;
- the potential cost/efficacy of adding a key information section in the context of EU legislation.

Like the PIL-S study, the PILS-BOX study was carried out by NIVEL and the University of Leeds. The evaluation was structured in three work packages, an extensive literature search, a European wide stakeholder survey and a SWOT-analysis [13].

Work package 1, the literature search was performed in several databases such as PubMed and Embase and resulted in 23 articles in international journals that met all inclusion criteria. In addition to the search for scientific literature, a search for so-called grey literature was carried out. For the latter, the Digital Repository Infrastructure Vision for European Research (DRIVER), Scirus and relevant websites, e.g. the EMA website, websites of national ministries of health of the MSs were searched. Three more reports were found [13].

The research team described some examples of key information sections in the literature, the *headline information* in the UK, the *Medicine Information Box* in Australia and the *Drug Facts box* and *Black Box Warnings* in the USA [13].

The introduction of a *headline information* was proposed in a report from the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. The MHRA-report “Always Read the Leaflet – Getting the best information with every medicine” [28] suggests adding a *headline information* in order to improve PLs and address the fact, that the length and apparent complexity of the PL may be an obstacle to read the whole leaflet. For details, refer to *Section 2.3.2.1*. According to this report, the *headline information* should be presented in a prominent place at the beginning of the PL and should summarise some key messages for safe and effective use of the medicinal product. It should also be ensured that the *headline information* is not too negative. Therefore, a balancing non-promotional statement of the indication should be included at the beginning of the section [28]. The research team of the PILS-BOX study found

two studies in the UK (scientific literature) that performed a user testing with a PL or SmPC containing a *headline information*. However, the only study that evaluated a PL with a *headline information* in a user testing concluded that the section did not improve the findability and comprehensibility of information in the PL. Furthermore, the investigated PL was found to be as difficult, well designed and useful as a PL without this section. Nevertheless, the participants of the performed user testing considered the *headline information* as an improvement. In the other study, that evaluated a SmPC with a key information section in a user testing, the HCPs indicated that a *headline information* on the front page of a SmPC is useful [13].

Black Box Warnings (BBW) are texts published by the Food and Drug Administration (FDA) that indicate serious to life-threatening risks associated with prescription-only medicinal products. If required, the FDA requests the MAH to include a BBW on the label or in the PL. The name *Black Box Warning* results from the warning text being surrounded by a black border. Although BBW are a kind of key information, they only show the negative aspects of the medicinal product, the risks and side effects. However, the EC should investigate the influence of introducing a key information section containing both information on the risks and benefits of a medicine. Therefore, the results on BBW can only be used to a limited extent. Nevertheless, it should be mentioned, that the scientific literature examined by the research team of the PILS-BOX study showed that the inclusion of a BBW generally leads to a decrease in the prescription frequency of the medicine. However, some studies also showed that if a medicinal product is prescribed, a BBW does not necessarily lead to an increase in patient care by the doctor. Thus, according to the studies considered, it is questionable whether a BBW actually leads to safer use of medicinal products [13].

The *Drug Facts Box* is displayed on the outer packaging of OTC medicines and was introduced by the FDA in 2002. A mandatory listing of important information in a certain order should help patients to compare OTC medicines better. According to FDA, a simple language should be used and certain layout details (sufficiently large font size and line spacing, use of bullet points, clearly marked sections) should be observed to ensure good readability. Therefore, according to the authors of the PILS-BOX study, the content and presentation of the *Drug Facts box* could serve as an example for a key information section in the PL [13].

The *Medicine Information Box* is used on labels of OTC medicines in Australia. It was proposed by the Therapeutic Goods Administration (TGA) – a division of the Australian Government Department of Health and Ageing – and is based on the *Drug Facts Box* of the USA. The TGA recommends which headings (“active ingredient”, “uses”, “warnings and allergy information”, “directions” and “storage information”) the *Medicine Information Box* should contain and in

which layout (white background, black text, information text: font height at least 1,5 mm, headings: font height at least 2 mm and in bold) the contents should be presented on the outer packaging. Hence, the content and presentation of the *Medicine Information Box* could also serve as an example for a key information section in the PL [13].

The research team of the PILS-BOX study also evaluated some scientific literature about benefit information and concluded that such information enhances patients` knowledge and assessment of the medicine. Patients are more satisfied with the information and rate the effectiveness and health benefits of the medicine as higher [13].

Overall, the authors of the PILS-BOX study concluded from the literature search that so far there is little evidence for the added value of including a key information section in the PL or SmPC, especially if the section contains both, information on the benefits and risks of a medicinal product. There is even less evidence for the feasibility and cost-effectiveness of including such a section [13].

In work package 2, the European wide stakeholder survey, patient organisations, HCP organisations, the pharmaceutical industry, regulatory officers and communication experts were consulted through an online structured questionnaire. The 118 participants came from all over the EU with an overrepresentation for the UK, the Netherlands, Sweden and Belgium. Response was low among all stakeholders, especially among HCPs and patient organisations. Firstly, stakeholders were asked whether they were in favour or against including a key information section. The following picture resulted for the PL: 67% of HCPs and 86% of patient organisations were for a general inclusion in all PLs, a little over 20% of HCPs were for an inclusion in selected PLs. The majority of the regulatory offices (56%) favoured the inclusion in selected PLs, but also about 30% were against an inclusion. Of the communication experts, about 50% were for a general inclusion and about 25% each for an inclusion in selected PLs or against an inclusion. The representatives of the pharmaceutical industry were the most divided in their opinions: just over 30% were for a general inclusion, just over 40% were against an inclusion and the rest was for an inclusion in selected PLs. The picture was similar for the SmPC: HCPs, representatives of the pharmaceutical industry and communication experts all arrived at similar numbers; only the regulatory offices changed the picture. Here, more than 50% were now against an inclusion of a key information section and less than 40% for an inclusion in selected SmPCs.* As far as layout is concerned, the majority of all stakeholders was in favour of adding key information in a text box at the beginning of the PL or SmPC.

* Note: The partially inaccurate percentages result from the fact that most of the data in the PILS-BOX study were processed graphically and not numerically

A majority of all stakeholders thought that warnings, contraindications and serious side effects should be included. Overall, only a minority of all stakeholders favoured the inclusion of benefit information in the key information section. A majority of stakeholders were in favour of limiting the number of points included in the key information section to 5-10. The participants of the survey were also in favour of referring to the different chapters in the PL or SmPC in the key information section. When the participants were asked what positive and negative effects the introduction of a key information section could have, they described as positive that people who do not normally read the PL could be encouraged to read at least the most important content. On the other hand, the inclusion of a key information section could also tempt not to read the entire PL, which would of course be negative. Moreover, the majority of HCPs and patient organisation representatives believed that an introduction of a key information section could improve safe use of medicines. Half of the regulatory officers believed this, whereas representatives of the pharmaceutical industry and communication experts were not convinced. Overall, the authors of the PILS-BOX study concluded from the European-wide stakeholder survey that there is no clear consensus among stakeholders as to whether a key information section should be introduced, what it should look like and what content it should contain [13].

Work package 3, the SWOT-analysis, outlined the strengths, weaknesses, opportunities and threats of adding a key information section for the safety and efficacy of the use of medicines. It was performed by the whole research team and based on the results from the literature search and the stakeholder survey. The limited evidence of added value of a key information section was identified as a weakness. One strength, however, was that the HCPs and patient organisations, i.e. the later users, are in favour of including such a section. Another weakness was that it is not clear what a key information section should look like and what content it should contain. The disagreement of the various stakeholders also poses a threat to the development process. However, it was seen as opportunity that examples from literature, such as from the UK or Australia, could be used as a basis. Another threat was that people who have previously read the entire PL may be tempted to read only the key information section and thus miss important information [13].

After completion of the three work packages, the authors of the PILS-BOX study formulated six recommendations to the EC, refer to *Annex 7.4*. The inclusion of a key information section should not be mandatory due to lack of evidence, but the inclusion of such a section tested by user testings should be allowed. In order to facilitate future inclusion of a key information section, experience should be gained from the introduction of the *headline information* in the UK and various key information sections which differ in layout and, in particular, content. The

different key information sections should be evaluated by user testings and more comprehensive studies should be carried out to assess whether the key information adds value and whether the reader is tempted to read more than the key information, e.g. by cross referencing. Finally, based on these results, criteria for the inclusion of information in these sections should be developed. Lastly, it was recommended to first examine the development and impact of key information sections in electronic versions of the PL or SmPC [13].

2.2.3 Report from the European Commission and EMA Action plan

The two external studies mentioned above were published by the EC on its website and were referred to MSs for consultation in April 2015 within the Pharmaceutical Committee. Based on this consultation and the contributions of the EMA, the EC finally published in March 2017 a report [29] outlining the current shortcomings of the SmPC and PL and making recommendations on how to improve them to better meet the needs of HCPs and patients. In accordance with Article 59 (4) of Directive 2001/83/EC, this report should be submitted to the European Parliament and Council by 1 January 2013 [5]. The delay was justified by the EC by the necessity to first carry out the two external studies and to consult the MSs on the results [29]. In its report, the EC formulated six recommendations which largely correspond to the recommendations of the PIL-S study and PILS-BOX study. For details, refer to *Annex 7.5*. In November 2017, the EMA proposed detailed steps, including a timeline for each EC recommendation in its Action plan. The EMA emphasized that resource planning would depend on Brexit and the associated relocation of the EMA [30].

In order to review the Readability Guideline, the SmPC Guideline and the QRD templates, and to develop a new guidance on translations, the EMA intended to involve all relevant stakeholders and academic experts. The latter should support the EMA with regard to benefit/risk communication, on linguistic matters, in the field of translations and the introduction of good information design principles. A timeframe of two years has been set as soon as resources would be available.

The EMA proposed to define precisely the scope of iterative user testing recommended by the EC in order to ensure that it complements the assessment by the applicant and thus adds value and avoids repetitions. The period should be 18 months, starting with the availability of resources.

The EMA required the development of criteria for the selection of best practice examples, the creation of an interactive website and a process for the maintenance of the online platform. All

European languages should be taken into account and the project should be fully implemented within one year, as resources would become available.

In order to examine how the new technologies could be used to optimise the presentation and design of PLs and SmPCs and how they could be integrated more into the care process, a joint EC/EMA multi-stakeholder workshop on product information and electronic media should take place in Q3 2018. It has already been carried out. For details, refer to *Section 2.2.4*.

The EMA suggested to implement and test the inclusion of a key information section in the European Public Assessment Report (EPAR) summaries of centrally authorised medicinal products. Based on the experiences gained, it should be examined whether adding a key information section is also feasible for the PL. All stakeholders and MSs should be involved in the discussion. The EMA proposed a period of two years starting with the availability of the necessary resources [29,30].

2.2.4 EMA/HMA/EC workshop on electronic product information (ePI)

In November 2017 the EMA launched a survey to provide an overview of the initiatives currently underway within the EU with regard to electronic package leaflets (ePLs) [31]. 38 projects have already been started within the EU, most of them from the pharmaceutical industry and NCAs. 14 of these projects were considered to be well established. Hence, it was assessed as urgent that the different initiatives within the EU were coordinated. On 28/29 November 2018 a workshop on ePI was held at the EMA premises in London [32]. In January 2019, the EMA published a report and the presentations of the workshop, as well as the „Electronic Product Information for Human Medicines in the EU – Draft Key Principles”, which was the main outcome of the workshop [31].

Some presentations held in the first session of the workshop discussed how the ePL could contribute to a better understanding of the PL by the patient and thus increase the safe use of the medicines. These presentations shall be discussed below.

Fakhredin Sayed Tabatabaei of the Dutch NCA (Medicines Evaluation Board, MEB) explained that reliable information on medicines was not easy to find on the Internet. At the moment the MAH submits the PI in a Word document to the EMA or NCA and the authorised PI is uploaded in different databases as PDF document. However, the text in a PDF document is unstructured, unlike an ePI where the content is electronically structured in different elements between which the user could easily navigate. Tabatabaei therefore demanded that a common EU electronic standard, an eQRD should be developed [31,33].

Kaisa Immonen from the European Patients` Forum (EPF) quoted a survey from 2014 in which six out of ten Europeans said they were looking for health information on the Internet. Therefore, the information should be of high quality. According to Immonen, the possibilities and advantages of ePI lie in its availability. Information in all EU languages is available anytime, anywhere, e.g. on mobile phones. On the other hand, it can also be adapted for people with disabilities, e.g. the text can be displayed in a larger font size. Another advantage is the extended information and functionality. The use of devices such as an inhaler can be explained by a video or visualisation, the search function can be used and individual medical terms can be explained by a glossary. One advantage for the safety of a medicinal product is that the information is up to date. The patient could be actively informed about new information by a message on his smartphone, if he has stored his medication in an app. Immonen also saw interactivity as an advantage, e.g. the ePL and eSmPC could be designed in such way that a side effect that has occurred can be reported directly to the responsible authority by clicking on a link. Nevertheless, the paper version of the PL should remain available for citizens with limited access to the Internet [31,34].

Sine Jensen from The European Consumer Organisation (BEUC) formulated some questions that should be answered before digitalisation. On one hand, it is important to clarify through which portal the information is provided and who monitors the quality of the information, and on the other hand whether all NCAs are able to implement digitalisation. According to Jensen, it is known that patients do not read the PL before taking a medicine. She therefore justifiably asked whether an ePL would improve this situation. Jensen also pointed out a possible risk for health inequalities. Does digital technology really improve access to health information/health services or does it disadvantage people who do not have access to the Internet? In her opinion, this consideration should focus primarily on older patients and those with low literate skills [31,35].

In the second session of the workshop an overview of the current initiatives in the EU regarding ePI was given and various projects from certain EU countries and Norway were presented. In the following, the projects in Spain, Norway and Germany will be described.

In Spain, there is the first NCA that has introduced ePI for nationally authorised medicines. The ePI is available for 85% of the nationally authorised medicines in Spain. According to César Hernández García of the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS, Spanish Agency for Medicines and Medical Devices), the advantages of the ePI are that it is easy to navigate, information can be found using the search function and links can lead to an

explanatory image or video. In addition, the information can be personalized and the patient can be alerted if changes are made [31,36].

In Norway, the NCA cooperates with a third party, the Norwegian Pharmaceutical compendium (Felleskatalogen). On the homepage of the Felleskatalogen, the user can display the so-called “FK text” for a certain medication, in which important sections of the SmPC have been prepared in XML format and in which it is easy to navigate. The patient can also use links to other official sites such as the WADA Anti-Doping List or excerpts from the Norwegian medication manual (Norsk legemiddelhåndbok), e.g. if the patient would like to be informed about active substance-related information for use in pregnancy or lactation. A photo of the dosage form is provided and some instruction videos explaining the application can be viewed. The entire PL can also be displayed, the individual sections of which can be read aloud. The user can put his medicines into a personalised list via the mobile phone app, which is also available, and is then informed by the Norwegian Medicines Agency (NOMA) about important safety issues and shortage situations in real time [37,38].

In Germany, there is a project called “Gebrauchsinformation 4.0 (Product Information 4.0)”, which is operated by a consortium from two trade associations (Verband der forschenden Arzneimittelhersteller (vfa) and Bundesverband der Pharmazeutischen Industrie (BPI)), the third party ePI provider Rote Liste Service GmbH, 18 pharmaceutical companies, patient organisations, the German NCAs Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and Paul-Ehrlich-Institut (PEI) and pharmacies/hospital pharmacies. The aim of the study is to develop a digital product information system for pharmaceuticals, where authority approved PI is widely available in a user-friendly electronic format. The PLs are converted to an electronic format (XML) and are provided via a mobile app, a website and a software link to pharmacies. The mobile app has an integrated function for a data matrix and barcode scan, the online website includes a print option as PDF. The project has been successfully evaluated by all stakeholders and additional services shall be developed in the future [39].

In the third session of the workshop, Elizabeth Scanlan (EMA) presented the work of a discussion group, consisting of NCA representatives from the HMA working group on Support for Better Use of Medicines from France, Iceland, the Netherlands, Norway and Spain. They had developed a list of features a future common EU standard for ePI should have and use cases that could be supported by an ePI, i.e. scenarios where the user interacts with the ePI. In order to increase the comprehensibility of the PL and SmPC or lead to a safer use of medicines, the ePI should have the following features. The ePI should be interoperable with e-health systems. Benefits for patients and HCPs could arise if the ePI were designed to work with other electronic

health systems, such as e-prescribing and dispensing, electronic health records, cross-border healthcare and clinical decision support systems for doctors. In addition, the ePL should be directly available, e.g. by scanning a barcode on the packaging. Furthermore, the navigation in the ePI should be user-friendly and a search function should be available. The ePIs should also integrate multimedia content, such as videos, e.g. on how to administer a medicine, or photos of the dosage form, e.g. tablets or capsules. In addition, the ePIs should be provided in such a way that people with visual impairments or people who cannot use a paper format, could still access the information. Furthermore, scanning a barcode on the package should allow the patient to display the PL in their preferred language, if an authorised PL in that language is available. It should also be possible for the patient to store its medication in a phone app that help patients to follow their dosage regimen correctly. The patient could receive a reminder of taking the medicine, and the administration could be explained in more detail in a video. Via interfaces, warning messages could inform the patient about updates, new safety information or recalls of his stored medicines. Finally, the ePI should contain links to additional relevant information, such as educational material or scientific assessment reports. HCPs may search ePIs of different medicines in the same indication to find a medicine that does not have a particular side effect, is lactose-free or can be used during pregnancy or lactation. Furthermore, the doctor could receive a message from his prescription system that there is new information in the ePI for the medicine that he wants to prescribe to his patient who is taking this medicine in the long term. Then the doctor could inform the patient about the new information. Furthermore, by clicking on a link in the ePI, the patient or HCP should be able to report side effects directly, which would facilitate the collection of real-world data [31,40]. At the end of the workshop the core document of the workshop, the draft key principles for ePI, were discussed. They include a definition of the ePI, some benefits for public health, that were presented by the discussion group and described above, and the statement that the ePI will not supersede but complement the paper-based PL [31,41].

2.3 Efforts in individual European Member States

2.3.1 Germany

2.3.1.1 Announcement by the BfArM

In 2006, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM, Federal Institute for Drugs and Medical Devices) published an announcement of recommendations for the design

of PLs and for checking the comprehensibility of PLs. The announcement was updated in 2015 and contains references to the QRD templates and the Readability Guideline as well as further recommendations for the design of PLs. These further recommendations are:

- the use of an active language style, by which patients are addressed directly;
- instructions for action should be described as precisely as possible and limited to the information that the user can actually implement;
- the language used should be simple and understandable for the average patient;
- technical terms should be translated into German, unless they are already part of general usage. Technical terms that are important for understanding may also be mentioned in brackets;
- bullets should be used to structure lists;
- repetition of content should be avoided.

In addition, the BfArM provides a German translation of the frequency convention for side effects stated in the annotated QRD-template. Furthermore, the BfArM points out that the layout is especially important with long, extensive PLs and should be checked by user testing in accordance to Section 22 (7) sentence 2 Arzneimittelgesetz (AMG, German Medicinal Products Act). The BfArM refers to the methods described in the Readability Guideline and specifies that user testing should be carried out in English in the decentralised and mutual recognition procedure. In the case of purely national procedures, however, user testing should be carried out in German [42,43,44]. Further information on user consultation can be found under Frequently Asked Questions (FAQ) on the BfArM website. The BfArM describes, inter alia, three methods which can be used for the user consultation. The structured oral interviews according to Sless and Wiseman, the written readability test according to Fuchs and an IT-supported analysis of the text according to a catalogue of numerous test criteria (without testing by laypeople) are described. The latter can only be used in certain cases with a meaningful justification [45].

2.3.1.2 Working Group AG Beipackzettel

In the Arbeitsgemeinschaft (AG) Beipackzettel (working group for package leaflets), founded in 2006, patient organisations, senior citizen associations and pharmaceutical companies work together to make PLs easier to understand and thus increase therapy safety. Members of the working group are, among others, the senior citizen association Bundesarbeitsgemeinschaft der Senioren-Organisationen e.V. (BAGSO), the patient organisation Deutsche Vereinigung Morbus Bechterew (DVMB) and the pharmaceutical company Pfizer as founding member.

Since 2006, more and more pharmaceutical companies have joined the working group, such as MSD, Novartis, UCB, Takeda and Abbvie. The AG Beipackzettel critically examines the content and design (layout, font, images, tables) of the member companies' PLs and attempts to make them more readable and understandable by means of a comprehensive revision. Thereby they follow a catalogue of criteria in which seven points are particularly important:

- a legible font should be used, as typography is important for the recognition of information;
- the information must be understandable by patients, that means the information must also be understandable for people without previous medical knowledge;
- the patient should be informed about the disease and the efficacy of the medicine. In the opinion of the AG Beipackzettel, the knowledge leads to high compliance with the therapy;
- the information should be presented in a structured and clear manner. This increases attention and makes it easier to find information;
- images and pictograms should be used as they increase the attention and comprehensibility by the reader;
- the most important information should be recognisable at first glance and should therefore be presented, e.g. in information or advice boxes;
- additional information on the medicine should be given. According to the AG Beipackzettel, this supports a health-promoting behaviour [46].

In 2018, the AG Beipackzettel published an article (Mühlbauer V et al.) pointing out that the information about the frequency of side effects in current PLs is misleading. In this study, user testing was performed with one standard PL and three alternative PLs of a fictitious medicinal product. The standard PL mentioned the frequency of side effects but did not explain that these side effects could also occur without taking the medicine. The alternative PLs contained information on how often side effects occur with and without medication and included a statement on the causal relation. The laypeople were asked questions about the general occurrence and causality of the side effects. According to the authors, readers of the standard PL could not distinguish what proportion of the listed side effects were actually caused by the medicine, or instead were symptoms that occurred independently of the use of medication. They overestimated the frequency of all listed side effects. Readers of the alternative PLs, on the other hand, were more able to answer to what extent the side effects were actually caused by the medicine [47].

According to its own statements, the working group AG Beipackzettel is also in exchange with health authorities, the German NCAs BfArM and PEI, European regulatory authorities and is

in talks with politicians. In addition, the AG Beipackzettel supports the PatientenInfo-Service of the Rote Liste Service GmbH, which is described in the following section [46].

2.3.1.3 The PatientenInfo-Service

The PatientenInfo-Service is a patient information service offered by the Rote Liste Service GmbH in cooperation with the Deutscher Blinden- und Sehbehindertenverband e.V. (DBSV, German Blind and Visually Impaired association). 34 pharmaceutical companies are partners of the PatientenInfo-Service such as Abbvie, AstraZeneca, Bayer, MSD, Novartis, Pfizer, Roche, Sanofi, Takeda, Verla and many more [48].

Pursuant to Article 56a of Directive 2001/83/EC and Section 11 (3c) of the AMG, MAHs are required to provide the PL in formats suitable for the blind and partially sighted at the request of patient organisations [5,42]. The PatientenInfo-Service offers the PLs of partner companies in four different formats:

- as Normal print PDF in DIN A4 format;
- as Large print PDF especially for the visually impaired in DIN A4 landscape format;
- as barrier-free website that can also be read out electronically;
- and as navigable audio book in DAISY format for the blind.

Blind and visually impaired people often use software that reads aloud the contents of websites or mobile apps. Since 2018, the PatientenInfo-Service has therefore been testing a barrier-free HTML-format that can be used with this software. Patients can download the new HTML files from the website and have their software read to them on their end devices. If the new format works well in the application, it will replace the audio book in DAISY (Digital Accessible Information System) format [48].

Furthermore, there is the project Gebrauchsinformation 4.0 (Product Information 4.0) in Germany which has already been described in *Section 2.2.4*.

2.3.2 United Kingdom

2.3.2.1 MHRA-report “Always read the leaflet”

As mentioned in *Section 2.2.2*, the MHRA published the report “Always Read the Leaflet – Getting the best information with every medicine” (ARTL) in 2005. The comprehensive report (173 pages) was prepared by the Committee on Safety of Medicines (CSM) Working Group on Patient Information [28].

Reading the ARTL, it can be noticed that some recommendations can also be found in the Readability Guideline. This is because some of the ARTL's recommendations were included in the Readability Guideline when it was revised in 2009. In order to avoid repetitions, only the points where the ARTL deviates from the Readability Guideline or where it contains further information will be described below.

Although Directive 2004/27/EC amending Directive 2001/83/EC, which makes user consultation mandatory and changes the order of information in the PL, should be implemented in Europe by 30 October 2005, the UK implementation date for new MAAs has been brought forward to 1 July 2005 [8,11,28]. A specific requirement is that the UK also demands user consultation for existing MAs. Accordingly, user testing for these PLs should have been carried out by 1 July 2008. Annex 5 of ARTL includes an example of how a user testing can be performed [28]. This example was almost identically included in the Readability Guideline in 2009.

According to the ARTL Annex 6, PLs should be well designed and clearly formulated so that as many people as possible can understand the information. People with limited English or reading skills and people with a certain degree of vision loss should also be considered. Annex 6 contains detailed information on how the information can be made understandable. Simple words with few syllables should be used, sentences should not contain more than 20 words and long paragraphs should be avoided. In addition, a list should not contain more than 5-6 bullet points. A serif font should be preferred as the font is easier to read and the font size of headings should generally be 14 pt., the font size of the main text 12 pt. PLs, e.g. for eye drops, which are likely to be read by visually impaired patients, should have an even larger font size between 16 and 20 pt. [28].

A comparison of the previous version with the currently valid Readability Guideline shows that many proposals from Annex 6 of the MHRA report have been included in the Readability Guideline as a result of the revision in 2009. However, the ARTL recommends an even larger font size than the 9 pt. recommended by the Readability Guideline.

In addition, Annex 6 of the ARTL contains recommendations on how visually impaired or blind people can gain access to information in PLs. The recommended formats are almost identical to those of the Readability Guideline. However, in the large print version a font size of 16-24 pt. instead of 16-20 pt. is recommended. In addition, the ARTL recommends the large print versions for patients with learning difficulties. The audiotope or CD versions are recommended for people with learning difficulties and people who understand the spoken word

better than written text. The PLs should contain a reference to the alternative formats in a font size of at least 14 points and in bold [28].

Furthermore, the ARTL includes “The information keys” which provides recommendations on how make the information of the PL available to people who cannot use the standard PL. The MAH should consider for which disease the medicine is intended or which groups of patients are likely to take the medicine. Then the MAH should consider whether this may cause problems as the information in the PL is not sufficiently accessible or understandable for them. For example, it could be eye drops that are likely to be used by people with vision loss or a medicine used for dementia and therefore mainly administered by carers. Or the medicine could be used mainly by older children. MAHs are therefore advised to consult patient organisations on how the information in the PL should be presented. In addition, posters in pharmacies are a way to inform people about the availability of PLs in different formats. Although the PL must be written in the official language of the MS, which in the UK means English, MAHs are encouraged to provide the leaflets also in another language if it is likely that people who do not speak English use the medicine. The use of “infomediarities”, which read and explain the PL to people who cannot read the printed version or helplines, whether it is recorded information or a live advice service, are options to help people with special access needs. The provision of additional leaflets is also recommended if, for example, a simplified PL could help specific patient groups, such as people with literacy and learning difficulties, limited English skills or older children, to better understand the information. Care must be taken to ensure that the simplification of the PL does not lead to a loss of information. In addition, videos could help to explain complex instructions or administration of a medicine, e.g. how to administer an inhaled medicine [28].

To promote the consistency in leaflets of different MAHs and to improve the comprehensibility of side effects, Annex 8 of the ARTL contains a glossary of medical terms in lay language. For example, Agranulocytosis is to be explained as “Severe reduction in the number of white blood cells which makes infections more likely” [28] or Vertigo is explained as “A feeling of dizziness or ‘spinning’” [28]. The list contained a total of 54 explanations in 2005 and should be expanded. Hence, principles for developing definitions are also included in Annex 8 [28].

To improve the communication of risks, Annex 10 of the ARTL contains a guideline on communication of risks and benefits. Qualitative or quantitative misinterpretation of possible side effects may result in the patient not making a rational decision about taking a medicine. Compliance problems due to exaggerated fear of side effects are one of many possible negative consequences of misjudgements about risks and possible benefits.

Firstly, Annex 10 advises to include a *headline information* with the most important key messages in a larger font size prominently at the beginning of the PL. Patients who, for whatever reason, do not read the entire leaflet should at least be informed about the safe and effective use of the medicine. However, readers of PLs should not be tempted to read only the *headline information* instead of the main text. On one hand, only the most important information should be presented as a short list with no more than about 2-6 bullet points and on the other hand a clear standard formulation at the end of the *headline information* should advise the patient to read the rest of the PL. Stating the date of the last revision of the leaflet should inform long-term users of the medicine whether they should re-read the PL. The most suitable types of information to be included in a *headline information* according to Annex 10 of the ARTL can be found in *Annex 7.6*. This includes “negative” information, such as contraindications, important drug interactions and side effects. To balance this, the first point should contain “positive” information about the medicine, limited to brief factual statements about the approved indication.

Secondly, Annex 10 of the ARTL provides further information on how to present the benefits of medicines. Only a few sentences (about 80 words or fewer) should be used. The MHRA recommends that information about the disease for which the product is prescribed be included and that this information be up-to-date, factual, informative and non-promotional. The benefit information may include, for example, why it is important to treat the disease, what could happen if the disease remained untreated, and whether it is short-term or chronic treatment. All information to be included can be found in *Annex 7.7*.

Thirdly, Annex 10 of the ARTL provides aid on how to present information about side effects. The PL should provide the patient with clear, understandable information about the risk of side effects and possible actions. In particular, patients should know whether they should continue to take their medicine and whether (and how urgently) they should seek medical advice about possible side effects. Careful attention to format and wording is needed to ensure that the information is comprehensive but not alarming. The severity and, if possible, the symptoms of all side effects should be described. Patients should be made aware of the fact that many side effects are dose-dependent. However, the formulation should be chosen in such a way that patients prescribed high doses would not be unsettled. The risk for side effects should always be quantified and stated numerically. Verbal descriptions should only be used if they are combined with statistical information [28]. The baseline risk should be stated and information such as “approximately”, “about” and “around” [28] should convey that there are inaccuracies in point estimates, e.g. “about 5 extra cancers for every 1000 patients treated” [28]. The MHRA

already specified in 2005 that only the upper limit should be specified when specifying frequency ranges, e.g. “fewer than 1 in every 1,000” rather than “between 1 in 10,000 and 1 in 1,000” [28]. Since version 8.0 this was also included in the annotated QRD template [22]. Finally, the MHRA points out that statistical risks are usually represented by a standard numerator of 1, e.g. “1 in 1,000” is compared with “1 in 10,000” [28]. However, according to MHRA, it may be more understandable for patients to present risks with the same denominator, e.g. “10 in 10,000” is compared with “1 in 10,000” [28].

2.3.2.2 Best practice guidance on patient information leaflets

In December 2014, the MHRA published the “Best practice guidance on patient information leaflets” (BPG-PL). The purpose of this guidance is to summarise all advice on PLs published by the MHRA and to supplement the ARTL [49].

Firstly, the BPG-PL refers to the QRD templates and informs that these templates should be followed. However, the BPG-PL stresses that the QRD templates do not contain any information on questions concerning the design and layout of the PL or the development of a patient-friendly language. Hence, MAHs must refer to the ARTL and the BPG-PL to maximise the quality of the full-colour mock-ups, which must be provided to the MHRA and are part of the marketing authorisation approval. The BPG-PL points out that it is very important to translate the information from the SmPC into colloquial English in order to be clear and understandable, as required by Article 63(2) of Directive 2001/83/EC. According to BPG-PL, many terms in the QRD template can be confusing. Hence, the MAHs are advised to consider more colloquial English for the UK. It is especially important to reword confusing headings or subheadings. Moreover, the BPG-PL recommends translating all information into lay language, to use short sentences or bullet points. Particularly, the MAHs should pay attention to the sections in the PL covering contraindications, warnings and side effects because these are often written in a too complex language [49]. Comparing the annotated QRD template version 10.1 with the BPG-PL, it is noticeable that the QRD template states that benefit information can be included after listing the indications “on a case-by-case basis [...] as long as it is compatible with the SmPC” and “useful for the patient” [3], while the BPG-PL states that this section “should include any benefit information considered appropriate” [49].

Secondly, the BPG-PL provides guidance regarding the design and layout of the PL. It is pointed out that a clear structure is very important for the reader to find his way around, as very few will read the PL from beginning to end. The BPG-PL recommends using enough white space within the written text, to use columns, as most readers are familiar with those through

newspapers and to consider an appropriate line length and line spacing. Regarding the minimum font size to be used, the BPG-PL refers to the Readability Guideline [49]. This is surprising, since in the ARTL a larger minimum font size was specified than in the Readability Guideline (12 pt. compared to 9 pt.).

According to the BPG-PL, headings are especially important because they show the reader where a section begins and help in understanding the information that follows. Hence, headings should briefly and concisely describe the following content and must be highlighted to make it easier for readers to find the information they are looking for. Highlighting can be achieved by using reverse text, i.e. white text on a dark background, larger font size and bold type cut, or larger font size in a highly contrasting colour. MAHs should consider older people, those whose first language is not English, people with learning difficulties and the visually impaired. If the medicine is taken by children and adolescents the information should be tailored to them and the PL should either refer to additional information sources or contain a tear off section in which the key messages for safe use are described in such a way that they can easily understand. When the medicine is administered in a hospital, the information intended for the patient should be separated from the information that concerns the hospital staff. A separate tear-off section for HCPs should contain the issues to consider when administering the medication [49]. Many of these recommendations are also listed in the annotated QRD template.

Thirdly, the BPG-PL provides further guidance on user testing according to Article 59(3) of Directive 2001/83/EC. Firstly, the MAH should clearly define the key messages for safe use of the medicinal product before testing. Secondly, the MAH should ensure that patient groups who are likely to use the medicine (including carers) are represented in the test subjects. It is sufficient for the participants to be able to imagine the condition for which the product is indicated. Users should not participate in such tests more than once every six months. HCPs must not be included to avoid bias. Thirdly, the MAH must carefully select the questions in user testing as these are evaluated by the assessors of MHRA to ensure that they reflect the identified key safety messages. Questions must be open and must not indicate where the answer can be found in the PL. In addition, the BPG-PL provides information on the success criteria that must be met to ensure that user testing has been carried out satisfactorily and how the report is to be prepared. Of course, user testing can only be performed with the full colour model and not with text versions, since the design and layout are crucial for the patient to find the key safety messages [49]. Finally, the BPG-PL defines in which cases user testings are always required and lists the same examples as in the Readability Guideline of 2009.

The BPG-PL also offers many examples and explanations as to when the applicant can refer to a PL that is similar in content, design and layout and has already been tested (bridging study). The last chapter of the BPG-PL deals with information, which is not required by law but which, in the opinion of the MHRA, may nevertheless be included in accordance with Article 62 of Directive 2001/83/EC. Besides benefit information, the BPG-PL recommends the inclusion of signposting to other sources of information. Principles set out in Article 62 of Directive 2001/83/EC must also be applied on the materials accessed via signposting in the PIL, i.e. the information must be compatible with the SmPC, useful for the patient and non-promotional. Sign posting can draw attention to information of patient organisations or general sources of medical information, to alternative formats for blind and partially sighted people, to additional company materials such as simplified leaflets, videos or leaflets in other languages. Finally, the BPG-PL recommends some information services for quality medical writing [49].

2.3.2.3 PIL of the month on MHRA website

Additionally to the two publications, the MHRA has also published best practice examples of well-structured and designed PILs on its website. Unfortunately, since the MHRA website moved to the GOV.UK website in 2015, these examples can only be found in the web archive [50].

2.3.3 Member States with multilingual package leaflets

Pursuant to Article 63 of Directive 2001/83/EC, the PL and the labelling have to be legible in the official language or languages of the MS in which the medicinal product is to be marketed. As a result, medicinal products in MSs, which have more than one official language, have multilingual labelling and PLs. According to the Readability Guideline, a clear distinction should be made between the different languages in multilingual PLs as well as outer and primary packaging, provided that there is sufficient space on the packaging. In addition, multilingual packages must contain the product name in Braille in all languages concerned. Furthermore, it must be ensured, particularly in the case of multilingual PLs, that the version to be checked in user testing is identical in colour, style, font size and paper to the one supplied in the original packaging [5,8].

Advice on multilingual packages is offered by some MSs/groups of MSs, and links to available information on Nordic packages, Baltic packages and Belgian packages can be found on the CMDh website [51]. The advice for Nordic packages is described below. The medicines agencies from Denmark, Finland, Iceland, Norway and Sweden have jointly published the

“Guideline on Nordic packages” and “Questions & Answers” concerning Nordic packages. A Nordic package is designed for at least two Nordic countries. A complete Nordic package includes all five languages on primary and outer packaging as well as on the PL. As in Finland the PL has to be printed in Finnish and Swedish, it is a good alternative to use an SE/FI package for Sweden and Finland and a DK/IS/NO package for Denmark, Iceland and Norway, which provides more space on the packaging. Some of the Blue-Box requirements* are the same in all five Nordic countries, e.g. the Nordic Article Number (Vnr) and the optional barcode or 2D code. It is therefore sufficient to print this information only once on the outer packaging. All Nordic countries except Denmark require mock-ups to be submitted prior to approval. MAHs can use a special form to request a joint mock-up assessment from the agencies concerned. In addition, MAHs can also address questions to the “Nordic package group” [52,53,54].

* Blue-Box requirements: additional information on labelling/package leaflet that may be required nationally according to Articles 57 and 62 of Directive 2001/83/EC [54]

3 Discussion

3.1 Directive, Guidelines and Templates

3.1.1 Have the amendments to Directive 2001/83/EC improved the comprehensibility of package leaflets?

Section 2.1.1 described the amendments to Directive 2001/83/EC that have been made regarding the SmPC and PL since 2001. In particular, the 2004 amendment introduced a number of changes that have contributed to improving the readability and comprehensibility of the PL and thus had a positive impact on user safety [1].

Firstly, the order in which the information must appear in the PL has been changed so that less important information has been moved to the end of the PL and important safety messages have been relocated to the beginning [1]. Since it is generally assumed that patients do not read the entire leaflet [28], it is even more important to mention important information first.

An essential step was also the introduction of user consultation in 2004 [1]. As described in *Section 2.1.4*, the user testing itself does not improve the comprehensibility of PLs. However, it can reveal deficiencies in existing formulations and thus lead to an improvement in the tested PLs in the short-term [8]. But also, in the long-term user testing can have a positive influence on **all** PLs, because according to the EMA, the results are also taken into account by the authorities in the development of their guidance documents such as the QRD templates [24], as mentioned in *Section 2.1.3*.

In addition, Article 56a has been introduced, which provides that, at the request of patient organisations, the PL should be made available in formats suitable for the blind and visually impaired [11]. If this requirement is implemented satisfactorily, it will in any case lead to a better comprehensibility of the leaflet for a specific group of people. *Section 3.4.1* deals with this issue.

Furthermore, Article 63(2) has been reworded to stress that the **design** of the PL is also important for comprehensibility and that the PL should enable the patient to **act appropriately**. Finally, Article 65 was strengthened in 2004 and the EC was mandated to publish **detailed** guidelines on readability [11]. Subsequently, the Readability Guideline was revised in 2009. Whether the revision of the Readability Guideline has been satisfactory, is discussed in *Section 3.1.2*.

With the amendment of Directive 2001/83/EC in 2010, the requirement that the EC should submit a report on the current shortcomings of the SmPC to the European Parliament was finally enshrined in law. For this report, all relevant stakeholders should be involved and finally proposals should be made on how the legibility and comprehensibility of the SmPC and the PL can be improved [14]. Moreover, it should be evaluated whether the addition of a key information section could improve the PL [13]. The EC has met this demand, albeit with a considerable delay. Two external studies were commissioned, the PIL-S-study and the PILS-BOX-Study, on which the EC based its proposed improvements. The results are discussed in *Section 3.2.1*

3.1.2 Does the Readability Guideline sufficiently support the comprehensibility of package leaflets?

The Readability Guideline from 1998 was fundamentally revised in 2009 due to numerous amendments made to Directive 2001/83/EC. The revision of the Readability Guideline clarified that user testing for medicinal products authorised from 30 October 2005 is now required by law and that MAHs are expected to submit the results of the evaluation in the MAA. In addition, more detailed information is given on cases where user testing must always be carried out and when it can be omitted by referring to a similar already approved PL. In contrast to the previous version, the revised Readability Guideline also contains precise information on how the results of user testing are to be presented to the authorities and defines how the authorities should evaluate these results. The revised version also describes the test method for user testing in much more detail, so that the MAH is better and more extensively supported. In addition, the revised Readability Guideline contains an additional chapter on alternative formats for the blind and visually impaired. The MAH receives detailed instructions on how to indicate the product name in Braille on the packaging and how alternative PL formats in large print or audio format can be provided [8,16].

It remains to be assessed whether the revised version of the Readability Guideline also provides sufficiently precise specifications in terms of layout and design and, above all, whether it also contains the correct specifications. There have been some improvements, e.g. the minimum font size has been increased to 9 pt. Times New Roman and an even larger font size, 16 to 20 pt., is recommended for medicines that are more likely to be used by the visually impaired [8,16]. However, the font size in PLs is repeatedly criticized, larger font sizes up to 12 pt. are requested and patient organizations even prefer a larger font size before a shorter PL [1]. Therefore, the

question arises whether the font size recommended by the Readability Guideline is not still too small.

In addition, it should also be considered that older age groups take most medicines [4]. Thus, it is not unlikely that the reader of the PL already has impaired vision because of eye changes such as presbyopia or a decrease in contrast vision due to cataract or retinal disorders such as age-related macular degeneration [55,56]. According to Fuchs et al. (2010), the optimal font size is between 9 and 11 pt., since even larger fonts would reduce usability of PLs because unwieldy formats would result [57].

The revision of the Readability Guideline also provides more precise information on which font type to use. Only easily readable fonts are recommended, in which problematic characters such as "i", "l" and "1" can be easily distinguished from each other. In addition, italics and underlining should not be used, as they are more difficult to read. On the other hand, the use of italics is allowed for Latin terms. This is especially odd considering the fact that foreign words should be avoided anyway, as patients do often not understand them. In addition, the Readability Guideline stipulates that capital letters may be used for highlighting purposes, although text in capital letters is more difficult to read and there are better ways of highlighting, such as a larger font or boldface [8,58].

It is positive that sufficient contrast, i.e. dark text on a light background must be ensured. However, the Readability Guideline also allows highlighting by using reverse type (i.e. light text on a dark background), even though this is significantly less readable. Moreover, the revision of the Readability Guideline recommends that no justification should be used. However, according to Fuchs et al. (2009), the use of justified text makes paragraphs significantly easier to read than text that is left aligned [8,58].

On the positive side, the Readability Guideline stresses the importance of the right wording and layout for headings, so that readers can orientate themselves in continuous text and quickly find answers to their questions. It also makes sense that the revision of the Readability Guideline continues to recommend an active style of writing and further stresses that no abbreviations should be used. In addition, medical terms should be translated and pictograms may be used as a supplement but should not replace the text. Another sensible recommendation by the guideline is that the author of a PL should consider the reader while writing, i.e. make sure that simple words with few syllables and simple sentences are used. This is the only way to ensure that people with reading difficulties and poor health literacy can understand the information. However, it is unfortunate that the definition of a long sentence from 1998 as a sentence of more than 20 words was deleted in the revision [8,16,58].

The revision of the Readability Guideline also no longer requires a minimum paper weight of 40 g/m² as in the previous version. Instead, it is pointed out that the paper must be thick enough and not glossy to avoid transparency and light reflection. However, this requirement allows much room for interpretation. On one hand, a general description can be sufficient and less restrictive, but on the other hand, a precise weight specification provides creators of the PL with a clear recommendation [8,16,58]. In addition, a study by Fuchs et al. (2015) showed that thicker paper or higher paper weight does not automatically lead to better legibility. The study revealed that different paper types with grammages of approximately 50 g/m² can show large differences in the impenetrability of light. According to Fuchs et al., the paper thickness should therefore be replaced by opacity, which is also recommended in the German DIN 1450. A minimum opacity of at least 80% is sensible and can also be achieved with thin papers, which prevents the leaflets from becoming too thick [59]. In another publication by Fuchs et al. (2015), it is criticized that according to the Readability Guideline, only uncoated papers should be used in order to minimize light reflection. The study explains that coated papers can be finished both matt and glossy. Thus, coated papers are not necessarily glossy and light reflecting. Moreover, they can show a significantly better opacity with a simultaneously lower thickness [60]. Therefore, preference should be given to thin, matt coated paper with high opacity, since the constantly increasing number of words and larger font sizes could lead to an oversized PL. This could subsequently lead to changes in packaging lines in the pharmaceutical industry and additional costs if the folded PL no longer fits into the folding boxes [59,60].

3.1.3 Are the QRD templates good as they are or can they be improved?

In the European-wide stakeholder survey conducted within the framework of the PIL-S study, some questions were asked about the QRD template version 8, which was valid at that time. The majority of respondents were of the opinion that no sections were missing and that the existing ones should be retained. The list of representatives of the MAH and the introductory paragraphs were the most cited sections to be omitted [1]. However, indicating the local representatives of the MAH has never been mandatory since its introduction into the QRD template [22]. A section on benefit information was most frequently mentioned as missing, but since version 8 of the annotated QRD template, MAHs have the possibility to include such information in the PL [1,3,22]. Furthermore, most stakeholders have agreed to keep the content and structure of the QRD templates as strongly regulated as the one assessed. Only representatives of the pharmaceutical industry would like more flexibility in terms of content

as they believe that different information should be highlighted for different medicines [1]. Subsequently, the EC also proposed to examine whether more flexibility could be allowed [29]. *Section 2.1.3* briefly describes the development of QRD templates since their introduction. The annotated version, which gives the MAH further explanations and advice, has been available since version 7.0 [22]. In addition, improvements are described, that were introduced into the QRD templates by the EMA based on user testing experience [24].

One could therefore assume that the QRD templates, which have been developed and improved over several years, are good as they are. Only the information box at the beginning of the PL should be removed and more flexibility could be given in terms of content.

However, a comparison of the individual versions of the QRD templates shows that their scope has increased since their introduction because more and more headings and standard statements have been introduced. This development is not in line with the demand from patients for shorter PLs [1,22]. In a publication by Wolf et al. (2014), the QRD template version 8 was compared with its predecessor and a shorter model template developed by the authors. From each of the three templates, three PLs were created with three texts for the active substance enalapril. The first text was the BfArM sample text for enalapril in German, the second text was a short version of the BfArM sample text and the third text was the English translation of the short version. According to the authors, the short versions still contained all information relevant for the patient. The PLs were tested by the same test subjects. For the shortened version in the model template, 93.2% of the German participants gave correct answers to content-related questions. Fewer participants gave correct answers to the shortened version in QRD template version 8 (91.1%) and in QRD template version 7.3.1 (87.3%). For the shortened version in the model template, 95.0% of the English participants gave correct answers. Again, fewer participants gave correct answers to the shortened version in QRD template version 8 (91.5%) and in QRD template version 7.3.1 (83.4%). The longer BfArM sample text was only tested in German. 80.4% of the participants gave correct answers to the BfArM sample text in the shorter model template. 81.2% of the participants gave correct answers to the BfArM sample text in QRD template version 8 and 76.2% in QRD template version 7.3.1. The authors concluded from the results that QRD template version 8 is an improvement in comparison to version 7.3.1 but still can be improved. The authors therefore recommended developing a shorter QRD template [61]. As described in *Section 2.1.3*, QRD template words specified in certain brackets ("`<text>`"[3]) can be selected or deleted as appropriate. Wolf et al. therefore recommended that only those QRD template words be included in the PL that are absolutely necessary until a shorter QRD template could take effect [61].

Nevertheless, the decision, which sections in the QRD template can be shortened or even removed remains difficult and thus will take time. Therefore, the emphasis should be set on making the existing QRD template as understandable and clear as possible. According to the Readability Guideline, long sentences should be avoided in the PL [8]. The Readability Guideline of 1998 defined a long sentence as a sentence with more than 20 words [16]. Hence, it is strange that some of the standard phrases in QRD Templates 10.1 consist of about 18 words and the sentence “If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine” [3] even consists of 29 words.

The annotated QRD template also states that it contains no instructions for the layout and design of the actually **printed** PL and refers instead to the Readability Guideline. In fact, the QRD template contains italics and underlining which should be avoided according to the Readability Guideline [3,8]. The question arises whether it is not confusing for the creators of PLs if type cuts are used in the QRD templates that should be avoided in the printed version of the PL. Moreover, it may be easier to get the information about content, layout and design of an easy-to-understand PL from one single document. It should therefore be checked whether good design of the PL could also be integrated into the QRD template.

The MHRA criticizes that the QRD templates are not written in good English [49]. In addition, my own experience with the German version has shown that the BfArM deviates partially from the official wording in the templates due to lack of comprehensibility. The MHRA BPG-PL even recommends reformulating confusing headings or subheadings of the QRD template and using more colloquial English to create a PL that is easy to understand [49]. However, since two representatives from each European MS participate in the working group preparing the QRD templates [20], the question arises as to why the national authorities need to recommend reformulating the wording of the QRD templates.

3.1.4 Consultation with target patient groups

As already mentioned in *Section 3.1.1*, the introduction of user consultation in 2004 led to an improvement in the comprehensibility of the individual PLs as well as the comprehensibility of PLs in general through the resulting adaptation of the QRD templates [8,24]. On the other hand, it can be said that the implementation of Article 59(3) of Directive 2001/83/EC does not go far enough. In most European MSs, only the PLs of medicinal products authorised after 30 October 2005 are subjects to user consultation. The Readability Guideline also requires user consultation only for these “newer” MAs. Only if there are significant changes to the PLs due

to a variation, a user consultation is also required for existing MAs [1,8]. However, it can be assumed that “older” PLs have the most misleading formulations. This begs the question whether these “older” PLs are the ones that should be examined. Of course, it could be argued that this would lead to an unreasonable effort for the MAHs. On the other hand, it often seems that the PLs of “older” medicines are not as detailed as those of “newer” ones. Therefore, it could be assumed that the resulting effort would be justified. In fact, the UK shows that a complete testing of all PLs is feasible. In the UK, user consultation must be carried out on all PLs, distinguishing between MAs submitted after and before 1 July 2005. In the latter case, the MAHs were given a longer period of three years to comply with this requirement [28]. In order to minimise the effort for the MAHs, it is recommended that references to already user tested PLs should be accepted by the competent authorities to the largest possible extent. Examples are listed in the Readability Guideline and the “Recommendations for Bridging” of the CMDh. Moreover, it is desirable that EMA and NCAs provide easily understandable reference texts for existing active substances. The MAHs could then adapt their PLs to the user tested reference text by submitting a variation. This would also have the advantage that the PLs of different MAHs would be uniform for existing active substances.

As described in *Section 2.1.2*, it is sufficient to test the PL in one EEA language and then faithfully translate it into the individual languages of the MSs in which the medicinal product is placed on the market. According to the Readability Guideline, the responsibility lies with the MAH in consultation with the MS or EMA [8]. Here the MAHs should be supported by a guideline. Therefore, the EC also recommends the development of a new guidance on translation that goes beyond the principle of faithful translation. This is considered to be very important as the lay language in the user tested PL must not be lost in translation [29].

Moreover, the EC recommends involving patients more in the development of the PLs by introducing an iterative user testing coordinated by the regulatory authorities. As proposed by the EMA, care should be taken to ensure that this new iterative user testing complements testing by the MAH and that duplication is avoided [29,30].

3.2 Recent efforts within the European Union

3.2.1 Can the PIL-S study and the PILS-BOX study contribute to improving the comprehensibility of package leaflets?

The PIL-S study and PILS-BOX study were carried out on behalf of the EC. The PIL-S study comprehensively examined the existing data on PL and SmPC deficiencies and formulated six

recommendations for improvements. The PILS-BOX study examined whether the introduction of a key information section could contribute to this improvement. In March 2017, four years later than planned, the EC finally published its report with six recommendations for improving the comprehensibility of PLs, which largely correspond to the recommendations of the PIL-S study and PILS-BOX study and are presented in *Annex 7.5*. Subsequently, the EMA Action Plan was published in 2017 [1,13,29,30].

The recommendations of the two external studies are meaningful and important. The PIL-S study and thus the EC report state that existing guidelines such as the Readability Guideline and the Packaging Information Guideline as well as the QRD templates should be thoroughly reviewed and adapted [1,29]. The PIL-S study concluded that current guidelines are considered not to be clear with regard to the recommendations for font sizes and line spacing [1]. However, looking at the Readability Guideline [8], it appears that concrete information on font size and line spacing is already available. Since the PIL-S study found that there is often demand for a larger font size and patients even prefer a larger font size to a shorter PL [1], it seems reasonable to recommend increasing the font size required by the Readability Guideline. Furthermore, it was pointed out in the discussion of the PIL-S study that the font size should rather be measured in terms of x-height than in points, since different fonts of the same point size can appear different in size [1]. A minimum x-height for immediate and outer packaging is already recommended in the Readability Guideline and is used for particulars prescribed on packaging of food supplements according to Regulation (EU) No 1169/2011 [8,62].

The x-height is the height of the lowercase x of a font, i.e. the distance between the baseline and the height of the lowercase x. As can be seen in Figure 1, the font size is the total vertical extent of a font with its ascender, x-height and descender, expressed in points (1 point = 0.352 mm). With the same font size measured in points, x-heights can deviate up to 40 % [63].



Figure 1: Explanation of font size and x-height based on a figure (presented in German) in a publication of the Deutscher Blinden- und Sehbehindertenverband e.V. (DBSV) [63].

The inclusion of a minimum x-height in the Readability Guideline is not explicitly recommended in the PIL-S study, but can be considered as reasonable.

In addition, it is useful to revise the QRD templates and remove unimportant passages, as it is repeatedly criticized that the PLs are too long [1]. It is positive that the PIL-S study and thus the EC recommend the development of a new guidance on translation so that MAHs are supported in translating the PL in order for the lay language not to be lost. It also seems reasonable that an iterative user testing, as described in *Section 3.1.4*, is recommended by the EC [29].

One of the most valuable recommendations of the PIL-S-study and thus of the EC-report is the demand that best practice examples of good, understandable PLs should be made available by the regulatory authorities via an online platform. The MAHs could then be guided by good examples. Another good recommendation is to investigate the extent to which the ePL could contribute to improving the comprehensibility of the contents of the PL [1,29]. The subsequent workshop at the EMA showed that there is potential in ePL and harmonisation within the EU is strongly recommended, as a number of different projects are already underway in the individual MSs [31].

Unfortunately, the PILS-BOX study does not offer a concrete recommendation as to whether a key information section should be included in the PL or not. According to the PILS-BOX study, the inclusion of a *headline information* in the UK did not lead to an improvement in the findability and comprehensibility of PL. However, the test subjects of the only study that investigated this were in favour of including the section. In addition, it is also an advantage if people who are deterred by the length of the PL at least read the key information section. In another study, the *headline information* of a SmPC was positively evaluated by the HCPs [13]. It is true that there is still little information available about the value of a key information section. However, if the key information section is not introduced, it will be difficult to gain this experience. Hence, it seems reasonable that the PILS-BOX study recommends that user tested key information sections should be allowed in PLs [13]. Furthermore, it is gratifying that the PILS-BOX study describes several key information sections, such as the *headline information* from the UK, the *BBW* and *Drug Facts Box* from the USA and the *Medicine Information Box* from Australia in detail regarding wording and design. These examples should be further developed and tested by user testings to create an ideal key information section [13]. Finally, there is no doubt that it is important that all European MSs are involved in improving the comprehensibility of the PL and the SmPC. Unfortunately, in both the PIL-S study as well as the PILS-BOX study, mostly Western countries were involved in the “European-wide” stakeholder surveys. This was probably due to the fact that the questionnaires were only written in English [1,13]. It seems difficult to justify this with lack of time or capacity as the studies

were funded by the EC which represents all MSs. In addition, the EC report based on the two external studies was published with a considerable delay.

3.2.2 Do alternative formats such as the electronic package leaflet offer a real improvement?

The workshop held at the EMA made it clear that there is potential in the ePL and that it can also contribute to improving the comprehensibility of the contents of the PL. Search functions can make it easier to find specific information. A glossary could explain medical terms or perhaps entire contexts in simpler words. New functionalities such as integrated user videos could support the correct use of medicinal products. An increase in the safety of medicine use could also lie in an individualised medicinal product app in which patients could store their medicines. The information in the app would always be up to date and not dependent on the time when the PL was placed in the packaging. If a medicinal product has a longer shelf life, different versions of the leaflet can circulate. If new side effects are added to the PL, the patient or doctor could be informed directly, just as he or she can be informed about recalls, counterfeits or shortage of medicines. The electronic versions also offer improvements for special patient groups such as the blind and visually impaired, as they can display the PL in large print or have it read aloud from e.g. their mobile phones. The ePL is also more suited to the growing globalization. If a traveller buys a medicine in a MS, which of course only contains the PL in the national language, he could have it displayed in his preferred language, e.g. by scanning a code on the outer packaging. In addition, a multilingual PL could be displayed by scanning such a code in an individual language. Despite all the advantages that an electronic version offers, it should not be forgotten that not all Europeans have access to the Internet and that the comprehensibility of the contents of ePLs must also be guaranteed. Nor is it clear whether more patients would read the leaflet if it were available electronically [31].

3.3 What do single Member States do and do some face special difficulties?

3.3.1 Germany

Section 2.3.1 described some efforts made by BfArM, AG Beipackzettel and PatientenInfo-Service. Please note that for capacity reasons it was not possible to address all initiatives within Germany. The branch associations of the pharmaceutical industry in Germany such as BAH, BPI or vfa are also very committed to making the PLs more comprehensible. Furthermore, in

March 2016, the Bundesrat (German Federal Council) passed a resolution to improve the readability of PLs. The resolution states that the PL contains important medical information for patients, but is difficult to understand for many people. Readers do not understand the medical terms, struggle to concentrate on reading a longer text or are unable to identify important information. Due to the small font size, older people in particular have problems reading the texts in the PLs. The Bundesrat sees the biggest problem in the fact that patients are unsettled by the numerous listed side effects. For this reason, the Bundesregierung (German Federal Government) should continue its efforts at European and national level to improve the readability of the PLs and to ensure that the recommendations of the BfArM, described in *Section 2.3.1.1*, are followed [64]. Thus, it has been shown that many efforts are being made within Germany, from the individual pharmaceutical companies to politics.

3.3.2 United Kingdom

Section 2.3.2 described some of the efforts made in the UK. The two MHRA publications, the ARTL and the BPG-PL, are comprehensive guidances. Among other things, the MHRA recommends the inclusion of a *headline information*, makes recommendations on how a benefit section in the PL should be structured and designed, and provides a glossary of patient-friendly descriptions of side effects for use by the MAHs. As described in *Section 2.3.2.1*, it is also striking that some of the information contained in the ARTL was initially only valid in the UK and was then adopted in 2009 when the Readability Guideline was revised at EU level. The UK is also demanding that the PLs of all medicines on the market must undergo user testing, going beyond the EU requirement. Moreover, the MHRA has also provided best practice examples of well-designed PLs on its website, which was recently requested by the EC report [28,29,49,50], discussed in *Section 3.2.1*.

It is obvious that the UK is very eager to improve the comprehensibility of PLs. One could even say that the UK has a certain leading role. It is still uncertain how the cooperation with the UK will develop after Brexit. In any case, the UK should definitely be included in the process of improving comprehensibility of PLs. Please note that for capacity reasons it was not possible to address all initiatives within the UK.

3.3.3 Member States with multilingual package leaflets

MAHs with medicinal products marketed in MSs with several official languages face special difficulties. The information on the labelling and PL must be available in all official languages, but according to the Readability Guideline, it must be ensured that general readability is not

compromised [8]. However, it does not seem necessary that the multilingual PLs be better divided into individual PLs in separate languages. According to the PIL-S study, only a minority of patient organisations was in favour of separate PLs in each language [1].

It should be noted that the CMDh website contains some links to further information on individual packages, such as Baltic packages, Belgian packages and Nordic packages. The analysis of the given information on the Nordic packages in *Section 2.3.3* [52,53,54], shows that the MAHs are widely supported by the countries concerned. As described in *Section 3.2.2*, countries with multilingual PLs in particular can benefit from the electronic PL. In addition, the PIL-S study recommends including MSs with multilingual PLs in the electronic media strategy [1]. It is well known that the Scandinavian countries are very advanced in terms of Internet access and use, e.g. in Norway the e-prescription has been made available all over the country in 2013 [65]. It should therefore be considered whether NOMA should be mandated to promote the development of the ePL in a leading role.

3.4 Specific patient groups

3.4.1 Are blind and visually impaired people adequately considered?

Pursuant to Article 56 a of Directive 2001/83/EC, MAHs are required to provide the PLs in formats suitable for blind and visually impaired people on request from patient organisations [5]. The Readability Guideline provides comprehensive information on how to meet the needs of blind and partially sighted patients through special PL formats such as large print and audio formats [8]. Whether these recommendations are implemented will be discussed using Germany as an example. In Germany, the PatientenInfo-Service makes PLs available in the formats recommended by the Readability Guideline. However, it is noticeable that although 34 pharmaceutical companies participate in this offer [48], not nearly all PLs for medicinal products marketed in Germany can be found on the website. It should of course be noted here that the law states that the MAH must provide the PL in such formats only “on request” [5]. But is it possible then to ensure that the patient gets the suitable format quickly and easily? Finally, one cannot expect a visually impaired or blind person to only use or get prescribed those medicinal products with PLs provided on the PatientenInfo-Service. The question arises whether the MAHs could be obliged to make the PLs of all medicinal products marketed in Germany available in such formats via the PatientenInfo-Service or a website of the BfArM.

3.4.2 Are people with poor health literacy and poor reading skills adequately considered?

The PIL-S study found that the identified PL deficiencies generally affect all patients, but those with poor health literacy are even more disadvantaged [1]. Unfortunately, the Readability Guideline gives little information on how to meet the needs of patients with low education. The Readability Guideline contains no further details apart from the recommendation that the PL should be clearly worded, well designed and that simple words with few syllables should be used and overly long sentences should be avoided [8]. It is obvious that these recommendations should also be followed in general, not only to meet the needs of patients with low literacy rates. Therefore, other publications were searched to help revise the PLs to better meet the needs of patients with poor reading skills or poor health literacy. Four of the publications found are discussed below.

As described in *Section 2.3.2*, the ARTL and BPG-PL of the MHRA provide further information on how to meet the needs of people with literacy and learning difficulties or limited English skills. As mentioned above, the MHRA recommends an additional simplified PL, the additional use of symbols and pictograms for better understanding, videos to explain complex instructions, and the establishment of helpline numbers to which patients can call if they have questions about their medicine [28,49].

The Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG, German Institute for Quality and Efficiency in Health Care), which provides health information for people in Germany on its website, commissioned external experts in 2014 to examine whether the information provided is also comprehensible to socially disadvantaged people. With the help of 28 selected test subjects, the experts examined, e.g. an article on asthma, a fact sheet on herniated disc and back pain, a flyer on HPV vaccination in girls and a film about middle ear infection in babies and children. Although no PLs were tested, some of the suggestions for improvements made by the experts may also be used to improve the comprehensibility of PLs. The word range of an average PL is within the range of the tested texts. The products tested are listed in Table 2 on the following page [66].

Product	Scope
Article: Asthma	ca. 12 300 words
Fact sheet: Herniated disc and back pain	ca. 3 200 words
Flyer: HPV vaccination-Info for girls (HPV: Human papillomavirus)	ca. 700 words
Film: Acute middle ear infection in babies and children	5:51 min

Table 2: tested products, based on a table (presented in German) in a publication of the IQWiG [66]

On one hand, the study found that the text-based health information was difficult to understand for the test subjects due to the scope and depth of the information. Some test subjects doubted whether the more comprehensive texts - the article on asthma comprised 28 pages - would be read in everyday life. Technical terms and foreign words were often not understood even if they were explained in the text. In addition, complex contents demanded too much of the test subjects. Percentages were misinterpreted and negated frequencies such as “less frequent” and “not uncommon” were difficult to understand. On the other hand, the structured text design with frequent paragraphs, subheadings and enumerations were appreciated. The test subjects wished for clear recommendations for action and a presentation close to everyday life. The film was very well received because the content was presented clearly [66].

The recommendations of the external experts were that the texts should be shorter (maximum 5 pages). In addition, a short overview in everyday language should be used to show the most important contents and clear recommendations for action. Images and pictures should be inserted for better understanding. Technical terms should be avoided and, if necessary, explained directly in the text. In risk communication, greater consideration should be given to personal involvement, e.g. through examples. Negation of verbal frequencies should be avoided. The focus should be more on the media format film, as this was rated very positively [66].

In a study from van Beusekom et al. (2016), 45 low literate patients were interviewed. It was investigated how this specific patient group use and evaluate the PL, how in their opinion the PL could be improved and especially how images can be used in a supportive way. The study found that most participants usually do not read the PL because it discourages them due to its length and small font size. The text should be a maximum of one A4 page long. They also stated that they would not understand the technical language and would be more likely to become insecure. Therefore, most rely on other sources of information such as talking to the doctor or pharmacist. According to the authors, the barrier to reading the PL can be lowered by

supporting short, structured texts with images. This would increase the interest in reading the text and the images could also explain the text and call to mind what has been read. Images could be used to highlight important topics, facilitate navigation and make the text clearer [67]. Taking into consideration the suggestions mentioned above, one possibility would be to provide an additional PL in a simplified language. However, people who would benefit from such a simplified PL might be inhibited from requesting it from the relevant pharmaceutical company or could not be able to access it on the Internet. Therefore, it should be considered whether a simplified PL should be made mandatory as a tear off section in the current QRD template. The simplified PL should be shorter than the standard PL and should use even simpler words and shorter sentences. In order to increase the comprehensibility, the use and dosage of the medicinal product should be explained by illustrations. Since people with reading difficulties often understand the spoken word better than written text, they could also benefit from a wide range of hearing formats or explanatory videos [28,49]. Consideration could also be given to whether throughout the European Union, e.g. health insurance funds should be instructed to set up a helpline that insured persons could call when they have questions concerning their medicinal product. Signposting to helpline numbers is very popular in the UK [28,49].

3.5 Is it possible to solve the frequently mentioned points of criticism?

3.5.1 Communication of side effects

It is often criticized that the large number of side effects listed in the PL leads to uncertainty in patients and therefore compliance problems. On the other hand, patient organisations feel that the patient must be fully informed and therefore all side effects should be listed, not just the serious and common ones [1].

When considering the legal side, the listed side effects are also intended to enable the patient to carry out a benefit-risk assessment. The absence of information on side effects can lead to the pharmaceutical company being held liable for damages incurred. Therefore, the patient must be informed about all side effects through the PL [68].

According to the annotated QRD template, side effects should be classified and listed according to their frequency. The frequency should be expressed in words and associated numerical data [3]. This is useful to enable the patient to estimate how likely a side effect is to occur. However, a review (Büchter et al. 2014) of 10 trials dealing with communicating the risk of side effects showed that both the verbal descriptors and the numerical data lead to an

overestimation of the risk. The overestimation was lower for the numerical data [69]. Unfortunately, even doctors and pharmacists often do not understand the frequency of side effects. In 2013, a written survey of 1000 doctors, pharmacists and lawyers was carried out in Germany in which the test subjects were to assign percentages to the German translations of the verbal terms for the frequencies “common”, “uncommon” and “rare”. It turned out that the percentages assigned by the test subjects were far higher than the probabilities assigned by the BfArM and thus the MedDRA Convention. From this, it can be concluded that the verbal terms of the frequencies in the PL do not correspond to the daily use of the terms. The authors of the review concluded that the verbal terms contained in the PL should be revised to better reflect the colloquial understanding of probabilities [70].

Mühlbauer et al. showed in 2015 that the majority of physicians (60-80%) as well as pharmacists and pharmacy students (66%) assume that the side effects listed are caused by the medicine in the frequency given in the PL. They do not take into account that most of the listed side effects are common symptoms in everyday life. 153 physicians and 87 pharmacists and pharmacy students were interviewed. The authors criticized that there is no notice in the PLs explaining that the listing of side effects does not necessarily mean that they are caused by the medicine [71].

In 2018, Mühlbauer et al. showed that laypeople have the same difficulties. With the currently used PLs, laypersons are not able to differentiate which part of the listed side effects are actually medicine-related side effects or rather symptoms that occur independently of the medication. This also leads to an overestimation of the frequencies and thus can lead to non-compliance with the medication. The authors also tested three alternative PLs that contained information on how often side effects occur with and without medication and included a statement on the causal relation. They were able to show that readers of the alternative PLs were better equipped to judge to what extent the side effects were actually caused by the medicine [47].

Hence, the listing of side effects in the PLs should be revised. On one hand, more appropriate verbal terms should be found expressing the numerical data. On the other hand, a notice should be included in the PLs explaining that the symptoms listed as side effects are not necessarily caused by the medicine. If possible, the patient should be shown how often the side effect occurs with placebo. However, even then it remains unclear whether the extensive listing of all side effects does not unsettle the patients too much.

3.5.2 Length of package leaflets

The size and length of the PL is repeatedly criticized. It is assumed that the reader is discouraged from reading the entire PL because of the large amount of information, the small print and the many technical terms [28,64]. The PL should aim to arouse interest, be easily understandable and ensure that important contents are grasped quickly. The patient should understand the purpose of the medication and at the same time be able to easily recognise possible side effects [64]. According to MHRA, it is therefore important to include a key information section at the beginning of the PL. The *headline information* should contain some key messages for safe and effective use. It is important to keep the section short to avoid patients relying on this section as a substitute for the entire text. The advantage of a key information section is that the patients do not have to extract key messages themselves. In addition, patients who do not normally read the PL can be encouraged to read at least a summary of the most important contents. An invitation at the end of the section asking the patient to read the rest of the leaflet is an attempt to ensure that patients who normally read the entire leaflet are not misled into not doing so. Moreover, it may be useful to mention the last revision of the PL at the end of the section. This way, long-term users can easily determine whether the PL has changed since they last read it [1,28]. Of course, an additional key information section extends the length of the PL even further. This criticism can be countered by the general demand that the QRD templates be revised. It should be attempted to remove passages that the patient does not necessarily need. Of course, it is difficult to decide which passages can be shortened. Possibly the model leaflet shortened by Fuchs et al. (2012) could be used as an example. In the shorter model template the introductory paragraphs were removed, the headings were formulated shorter and more concisely, the sentences were shortened and repetitions were avoided [72]. It was also used in the study by Wolf et al. (2014) cited in *Section 3.1.3* [61]. Since the list of side effects is often very long, one could come up with the idea of starting here and naming only the most important side effects. However, as mentioned in *Section 3.5.1*, this is not possible because patients expect information on all side effects and MAHs are also obliged to provide it for liability reasons [1,68]. The most important thing, however, is probably to lower the inhibition threshold to read the long text. Therefore, according to the study by van Beusekom et al. (2016), which actually aimed at low-literate patients, attempts should generally be made to make the leaflet as interesting as possible. Pictograms, symbols, illustrations, and a clear text structure could contribute to this [67]. Nevertheless, there will always be people who will not read the leaflet due to mental overload and disinterest.

4 Conclusion and Outlook

The readability and comprehensibility of PLs is repeatedly criticized. However, as stated in the Discussion, enormous efforts have been made to increase the comprehensibility of PLs. These efforts have been made by all stakeholders, including politicians, regulatory authorities, pharmaceutical industry associations, pharmaceutical companies, user testing companies and patient organisations. Particularly with regard to the comprehensive guidelines established at national and EU level, huge efforts have been made to make the PL more readable and understandable. Finally, this chapter outlines the context in which laws and guidelines can be considered sufficient and in which context they can still be improved. The aim is to make recommendations as to what these improvements could look like.

Directive 2001/83/EC

It is concluded that the legislation, in particular Directive 2001/83/EC, provides a sufficient legal framework to ensure that the PL is readable and comprehensible. The Directive prescribes a specific order in which important safety information is mentioned first and less important information can be found at the end of the PL. Moreover, the PL must be written and designed in such a way that it is legible and understandable for the patient. Since 2005, the comprehensibility of PLs must be checked by user consultation with target patient groups. In addition, special formats suitable for visually impaired and blind patients are required by law. The obligation to conduct the user consultation should be extended to all existing marketing authorisations, as it is expected that the PLs of medicinal products authorised before 30 October 2005 in particular will need to be improved. However, it does not appear necessary to amend the Directive in this regard. The Readability Guideline seems to be the appropriate document to be amended in this area.

The requirement for a key information section at the beginning of the PL should be included in the Directive, as patient organisations are in favour of including such a section and it is repeatedly doubted that patients read the entire PL. This key information section should contain important safety information and information on the benefits of the medicine.

In addition, it should be considered whether the Directive should additionally require simplified PLs to be made available to people with reading difficulties or poor health literacy.

Readability Guideline

The details of the above mentioned additional legal requirements should be described in the Readability Guideline.

As regards user consultation, the requirement should be extended to all existing MAs, including those authorised before 30 October 2005. In addition, any change in the wording of an already user tested PL should lead to further testing, as the quality of the PL should not decrease during the lifecycle of the medicinal product.

The Readability Guideline should contain details on the information and design of a key information section. Ideas can be drawn from the key information sections already in use in the UK, the USA and Australia.

The Readability Guideline should be much more detailed on how to address the specific needs of people with low health literacy and poor reading skills. A simplified PL should be introduced. The simplified PL should be even shorter than the standard PL and clearly structured through bullet lists, supported by explanatory illustrations. In this way, the inhibition threshold for reading the text could be lowered. Since people with reading difficulties often understand the spoken word better than written text, they could also benefit from a variety of audio formats or explanatory videos.

In summary, the current Readability Guideline provides quite detailed information on design and layout to ensure understandable PLs. However, some recommendations should be reconsidered or removed. Consideration should be given to increasing the minimum font size from 9 pt. to 11 pt. as the small font size is repeatedly criticized and most of the medicines are administered to elderly people who may suffer from vision loss. An even larger font size does not seem reasonable, as unwieldy formats of the PLs would result. Furthermore, it is better to define the minimum font size using the x-height, since different fonts of the same point size can appear different in size. In addition, more precise requirements should be set for the wording and the maximum length of sentences in order to further increase the quality and thus the comprehensibility of the PLs. As in the 1998 Readability Guideline, a maximum number of words in a sentence should be defined. Consideration should be given to whether the requirements should be even stricter than the previous maximum of 20 words.

According to the Readability Guideline, italics should not be used due to their poor legibility. The exception for Latin terms should be removed from the Readability Guideline, as foreign words should be avoided anyway and will certainly not be better understood when written in italics. It is better to use a lay term and, if absolutely necessary, to put the foreign word in

normal font and in brackets directly behind it. The use of capital letters for highlighting should also be removed from the Readability Guideline, as there are better ways of highlighting, such as using a different colour or bold type cut. The indication that no justification may be used should also be deleted, as the use of justified text significantly improves the legibility of paragraphs compared to texts that are left-aligned.

Finally, the requirement that the paper of the PL should be thick enough to avoid transparency should be changed to a minimum opacity. Since thin, matt coated paper has many advantages, the indication that no coated paper may be used should be removed from the Readability Guideline.

QRD templates

With regard to the QRD templates, it can be concluded that they should be thoroughly reviewed, shortened and clarified. As the revision of the QRD templates has added more and more standard statements, the volume of the QRD template has increased significantly. This fact does not correspond to the wish of many patients that the PL should become shorter. On the other hand, patients expect to be fully informed. Hence, it is difficult to decide which passages can be shortened or even removed from the QRD templates. It should be started with the introductory paragraphs and the indication of all package sizes being strongly shortened or omitted. All stakeholders should be involved in these considerations. Until a shorter QRD template has come into effect, MAHs should try to make the leaflets as short as possible by using the bracket convention of the QRD template.

In addition, the focus should be on making the existing QRD template clearer and more understandable. The standard headings and statements must be kept much shorter. It seems especially important to rephrase standard sentences which contain many subordinate clauses and thus are very long. Moreover, the headings and standard statements in all 24 available languages should be reworded to ensure understandable colloquial language. Otherwise, people with poor reading skills have no chance of understanding the PLs. It seems even better to introduce a specific simplified PL, as described above, as a tear off section in the QRD template. Furthermore, the QRD template should also describe how a key information section can be included in the PL. The UK headline information should be used as a reference. A certain risk that the patient will only read the key information section will always remain. Therefore, it seems particularly important that a final standard sentence in larger font indicate that the patient should also read the rest of the PL. Cross-references to the individual chapters of the PL appear to be very useful in encouraging the reader to do so.

Finally, the used type cut in the QRD template should be reconsidered. Since italics and underlining should be avoided according to the Readability Guideline, they should also be removed from the QRD template. Moreover, it is desirable that the information from the Readability Guideline and the QRD template be combined into a single guidance. If stakeholders conclude that this is not feasible, the two guidances should at least not contradict each other.

Communication of side effects

It is obvious that not only the standard statements in the QRD template have to be shortened and formulated more clearly. In particular, the individual text “filled” in the QRD templates must be structured more clearly and formulated simpler. In order to improve risk communication, the NCAs of all European MSs should publish glossaries with side effects that are explained in lay language. The NCAs can be guided by the MHRA glossary.

In addition, the list of side effects in the PLs should be revised. On one hand, more appropriate verbal terms than “common”, “uncommon” and “rare” should be found to express the numerical data. On the other hand, the PLs should indicate that the symptoms listed as side effects are not necessarily caused by the medicine. If possible, the patient should be informed how often the side effect occurs with placebo. A QRD standard sentence should be developed to inform patients that the side effects listed in the PL may be caused by the medicinal product, but may also be symptoms that occur independently of the medicinal product.

User consultation with target patient groups

As mentioned above, the requirement to perform user consultation with target patient groups should be extended to all MAs, including those approved before 30 October 2005.

In order to minimise the workload for the MAHs and avoid duplication, the NCAs of all European MSs should develop well designed, user tested reference texts of existing active substances. In this way, the MAHs have the possibility to adapt their PLs to the reference text by submitting a variation.

In order to further involve patients in the development of an understandable wording and design of the PL, the iterative user testing proposed by the EC should be introduced. As proposed by the EMA, care should be taken to ensure that this new iterative user testing complements the testing done by the MAH and that duplication of work is avoided.

Finally, it can be said that a lot has been done so far to obtain easily understandable PLs. However, as described above, many more improvements can still be made.

The recommendations compiled and developed in this thesis are listed in *Annex 7.8*.

5 Summary

Each medicinal product in the European Union contains a package leaflet. The purpose of the package leaflet is to inform the patient how to use the medicine appropriately and safely.

The information about the therapeutic indication and possible side effects should enable the patient to make a well-informed decision. However, the legibility and comprehensibility of the package leaflet is repeatedly criticized. Often the font size appears too small, the length too extensive and the listing of the many side effects too unsettling for the patient.

This thesis intended to examine and summarise the efforts that have been made within the European Union to ensure the readability and comprehensibility of the package leaflet. In this context, the changes that have been made to laws, guidelines and templates so far were examined. Furthermore, the recent efforts of the European Commission, the European Medicines Agency and selected national competent authorities were described.

It has been found that enormous efforts have been made so far to increase the comprehensibility of package leaflets. These efforts have been made by all stakeholders, including politicians, regulatory authorities, pharmaceutical industry associations, pharmaceutical companies, user testing companies and patient organisations. Particularly with regard to the comprehensive guidelines established at national and EU level, great efforts have been made to make the package inserts more readable and understandable. However, there are still ways to make them more comprehensible. The discussion therefore focused on opportunities for individual stakeholders to contribute and on how the existing guidelines could be improved.

It is concluded that Directive 2001/83/EC provides a comprehensive legal framework for the readability and comprehensibility of package leaflets. However, the Directive should allow for the inclusion of a key information section in the package leaflet, containing important safety information that is reconciled with information on the benefits of the medicinal product. The Readability Guideline should extend its requirement for user consultation with target patient groups to all existing marketing authorisations and can be improved with regard to its design and layout recommendations. The QRD templates should be thoroughly reviewed, shortened and unimportant passages removed. The standard headings and standard statements contained in the QRD templates should be simplified and rephrased in colloquial language. In addition, communication of side effects should be revised and the needs of people with poor reading and health literacy should be better addressed.

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7 Annexes

7.1 Article 11 of Directive 2001/83/EC

Article 11

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

1. name of the medicinal product followed by the strength and the pharmaceutical form.
2. qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.
3. pharmaceutical form.
4. clinical particulars:
 - 4.1. therapeutic indications,
 - 4.2. posology and method of administration for adults and, where necessary for children,
 - 4.3. contra-indications,
 - 4.4. special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,
 - 4.5. interaction with other medicinal products and other forms of interactions,
 - 4.6. use during pregnancy and lactation,
 - 4.7. effects on ability to drive and to use machines,
 - 4.8. undesirable effects,
 - 4.9. overdose (symptoms, emergency procedures, antidotes).
5. pharmacological properties:
 - 5.1. pharmacodynamic properties,
 - 5.2. pharmacokinetic properties,
 - 5.3. preclinical safety data.
6. pharmaceutical particulars:
 - 6.1. list of excipients,
 - 6.2. major incompatibilities,
 - 6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,
 - 6.4. special precautions for storage,

- 6.5. nature and contents of container,
- 6.6. special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate.
7. marketing authorisation holder.
8. marketing authorisation number(s).
9. date of the first authorisation or renewal of the authorisation.
10. date of revision of the text.
11. for radiopharmaceuticals, full details of internal radiation dosimetry.
12. for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

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

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

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system referred to in Article 107a (1). Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of Article 107a (1). [5]

7.2 Article 59(1) of Directive 2001/83/EC

Article 59

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

- (a) for the identification of the medicinal product:
 - (i) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the product contains only one active substance and if its name is an invented name;
 - (ii) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;
- (b) the therapeutic indications;
- (c) a list of information which is necessary before the medicinal product is taken:
 - (i) contra-indications;
 - (ii) appropriate precautions for use;
 - (iii) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;
 - (iv) special warnings;
- (d) the necessary and usual instructions for proper use, and in particular:
 - (i) the dosage,
 - (ii) the method and, if necessary, route of administration;
 - (iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;
and, as appropriate, depending on the nature of the product:
 - (iv) the duration of treatment, where it should be limited;
 - (v) the action to be taken in case of an overdose (such as symptoms, emergency procedures);
 - (vi) what to do when one or more doses have not been taken;
 - (vii) indication, if necessary, of the risk of withdrawal effects;
 - (viii) 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). [5]

7.3 Recommendations of the PIL-S study

Recommendations to the European Commission

Based upon the above the following recommendations are made:

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

7.4 Recommendations of the PILS-BOX study

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. [13]

7.5 Recommendations from the European Commission

Report from the Commission to the European Parliament and the Council

Brussels, 22.3.2017, (COM(2017) 135 final)

Recommendations

1. Generally, there should be more focus on improving the PL rather than the SmPC. However, for any potential improvement of the PL it should be also considered whether a corresponding or related change of the SmPC would be appropriate.
2. It should be considered to revise the existing guidelines, in particular the Readability Guideline, the Packaging Information Guideline and, where appropriate, the SmPC Guideline to include principles of good information design and consider allowing more flexibility in the information recommended in the QRD template, as long as the relevant legislation allows it. These revisions should also include introduction of guidance on translations that go beyond the principle of faithful translation. The aim should be to ensure that the lay language introduced through user testing in the original language version is not lost during translation.
3. The input from patients during the process and the related methodology should be further improved, for example, by considering the requirement to make the user testing process more iterative and to ensure that a sufficiently mature version of the PL is user-tested. This iterative user-testing would be coordinated by regulatory authorities in parallel to the assessment in a way that does not disrupt the whole marketing authorisation process. The iterative testing should focus on the content of the PL, rather than the format and layout, to ensure that information is clear and written in a way which is easily understood by patients. Potential amendments of the Readability Guideline could be considered in this respect taking also into account the use of structured benefit-risk approaches and visual representations to communicate benefits and risks to different stakeholders in different situations, including those approaches developed by the European Medicines Agency in the context of the Benefit-Risk Methodology project and by the Innovative Medicines Initiative (IMI) Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project.
4. Best practice examples of aspects of the PL (and the SmPC) design could be made available for pharmaceutical companies on a platform that would be suitable for that purpose and that could be regularly updated. These examples should include not only the end products, but

also information on the process of development, where possible. The selection of these examples should be evidence-based.

5. It is recommended to explore the use of electronic media to provide the information included in the SmPC and PL in the future. It should be further explored what opportunities new technologies offer to optimize the presentation and design of SmPC and PL. In this context the opportunities for the information included in the SmPC and the PL to be more easily used as an integrated part of the care process should be explored. For example, developing mechanisms through electronic tools to inform patients and healthcare professionals on changes in the SmPC and PL should be considered. The exploratory work in this area should be based on and further develop the existing work done by the European Medicines Agency in this area and should follow a multi-stakeholder approach involving also the pharmaceutical industry, patients, consumers, healthcare professionals, the Member States and the Commission. The aim will be to develop the key principles for the use of electronic SmPC and PL formats. The results of this exploratory work should be submitted to the Commission for any follow-up action as appropriate.
6. More evidence would need to be gathered before considering introduction of a key information section in the Product Information. It is suggested to continue further exploratory work on the use of such key information in the PL as well as the possibility to use Quick Response (QR) codes as another way to make available information to patients. Appropriate testing (e.g. user testing) could be a way to demonstrate the clear evidence of the usefulness and added value to patients to introduce a key information section in the PL. In this respect, the work currently being undertaken by EMA as part of its strategy to improve information on benefit-risk to patients and healthcare professionals could be taken into account. In particular, the planned testing of adding a 'key information section' to the 'EPAR summary' for each centrally authorised medicinal product could be used for this purpose. This may help to decide on the type of information that should be provided in the PL and the category or type of medicines where such a key information section could be useful and appropriate. [29]

7.6 **Headline information according to the MHRA**

Most suitable types of information for inclusion

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; or
- where to find further information. [28]

7.7 Presenting the Benefits of medicines according to the MHRA

The section 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 (ie 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. [28]

7.8 Recommendations compiled and developed in this thesis

Recommendations for Directive 2001/83/EC

1. The requirement of a key information section at the beginning of the package leaflet should be included in the Directive. This section should contain important safety information, supplemented with information about the benefits of the medicine.
2. Consideration should be given to the inclusion of a requirement in the Directive to provide a simplified PL for people with reading difficulties and poor health literacy.

Recommendations for the Readability Guideline

1. The requirement to perform user consultation with target patient groups should be extended to all marketing authorisations including those approved before 30 October 2005.
2. Details on the design and information contained in a new key information section should be introduced.
3. Efforts should be made to better address the specific needs of people with poor reading skills and low health literacy. It should be recommended that a simplified package leaflet and hearing formats be made available on request. It should be recommended to include explanatory illustrations.
4. The minimum font size should be increased from 9 pt. to 11 pt., while a definition of a minimum x-height would be even better.
5. Detailed guidance on the wording and maximum lengths of sentences should be provided. Subordinate clauses and sentences longer than 15-20 words should be avoided.
6. Italics should generally be avoided, even for Latin terms.
7. Latin terms should be avoided. If they are absolutely necessary, they should be displayed in normal font and in brackets behind an explanation in lay language.
8. The option of using capitals for highlighting should be removed.
9. The recommendation not to use justified text should be removed.
10. The requirement that the paper should be thick enough to avoid transparency should be removed. There are better ways to ensure light impermeability, e.g. with minimal opacity. The use of thin, matt coated paper should be allowed.

Recommendations for the QRD templates

1. All stakeholders should be involved in the revision, shortening and clarification of the QRD templates. The introductory sections and the indication of all package sizes should be removed.

2. The standard headings and statements should be shortened and reformulated to make them easier to understand. Standard statements should not contain more than one subordinate clause.
3. The standard headings and statements of all 24 available languages should be reformulated to ensure colloquial language.
4. The content and design of a key information section should be defined. A final standard sentence in larger font should invite the patient to read the rest of the leaflet. The use of cross-references may further encourage the reader to do so.
5. No italics or underlining should be used in the QRD template.
6. A simplified package leaflet should be developed as a tear-off section in the QRD template.
7. A QRD standard sentence should be developed to inform patients that the side effects listed in the package leaflet may be caused by the medicinal product, but may also be symptoms that occur independently of the medicinal product.

Communication of side effects

1. The national competent authorities of all European Member States should publish glossaries of side effects in lay language. Marketing authorisation holders should follow these glossaries.
2. New, more appropriate verbal terms than “common”, “uncommon”, and “rare” should be defined for the expression of numerical data.
3. A QRD standard sentence should be developed to inform patients that the side effects listed in the package leaflet may be caused by the medicinal product, but may also be symptoms that occur independently of the medicinal product.
4. If possible, patients should be informed how often symptoms/side effects occur with placebo.

User consultation with target patient groups

1. The requirement to perform user consultation with target patient groups should be extended to all marketing authorisations including those approved before 30 October 2005.
2. National competent authorities should develop well designed, user tested reference texts for existing active substances. Marketing authorisation holders should be able to adapt the text of their package leaflets to those reference texts by submitting a variation.

Am Ende:

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

München, den 25.10.2019

Theresa Sorgenfrei