Package Leaflets: Testing and Harmonisation

in relation to the overall business process in regulatory procedures

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An example of the impact of changing regulatory requirements

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Scope of Thesis:

Package leaflets (PLs) are addressed to the user, mostly the patient, and must accompany medicinal products in Europe. Their intention is to give factual, supportable, understandable, and appropriate information to the user in such a way as to allow him to decide whether he wishes to receive therapy.

Directive 2004/27/EC comprises several substantial changes to the regulation of medicinal products in Europe. There are two PL related new obligations:

- *The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority* (*Directive 2001/83/EC as amended Art 61 (1) 2nd sentence*) *... to ensure that it* (the PL) *is legible, clear and easy to use*
- The PL and the labelling will be harmonised in decentralised procedures for all concerned countries (*Directive 2001/83/EC as amended Art 28*).

These requirements have a profound impact on the business processes of the pharmaceutical industry as well as on the content and format of PLs.

The present thesis aims to elucidate the two new legal requirements on PLs that are closely connected to each other. Emphasis is given on the situation of mutual recognition procedure (MRP) products that already had been approved when the transition period of the *Directive 2004/27/EC* ended ('established' MRP products).

These 'established' MRP products have PLs, which were nationally written and approved before the enforcement of the new obligations. However, as the new requirements apply at least partly retroactively, there is a resulting need for European-wide harmonised, tested, translated, and approved PLs. This highly demanding, complex situation is dismantled and analysed in this thesis.

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1 Introduction

Package leaflets – Just another piece of paper?

According to pertinent law medical therapy is an assault on the patient, even when successfully accomplished. Historically in the field of surgery the term '***informed consent'*** was used as a means to allow the surgeon to act within the law. A valid informed consent is a form signed by the patient before surgery stating that he was informed by the physician (i.e. the surgeon) about the risks involved and agrees to this medical therapy regardless.

In principle, this scheme is also true for therapy by means of medicinal products. However, the process to secure an 'informed consent' of the patient is different, and therefore should be better distinguished by use of the term ***pharmaceutical informed consent.***[1] European law postulates a shared responsibility between the (prescribing) physician and the Marketing Authorisation Holder (MAH) for providing information to the patient. This information has to be provided in such a manner that it enables the patient to decide whether he agrees to this therapy or not.

Pertinent perception of the duties involved is that in a two-step process the physician has to first explain on a general level the patient specific risk-benefit profile of the prescription. In the second step the MAH explains the general risk-benefit profile of the medicinal product. The physician talks directly to his patient, whereas the MAH communicates with the patient by means of the PL. On the 'physician level' the patient agrees to the prescription. On the 'MAH level' the patient gives his '*pharmaceutical informed consent'* to the therapy by the act of 'taking' or 'using' the medicinal product.

Overall in Europe, PLs play an important role in the decision making process for the patient and it is of utmost importance that they can be clearly understood. In the European legal environment with the overhanging threat of legal liability the MAHs of course are also highly concerned that this need for comprehensibility is met.

1.1 Overall European legal history on PLs and PL-testing

In the following the legal roots and developments of the European legislation governing the requirement for harmonised PLs and labelling as well as PL-testing are briefly summarised with focus on MRP relevant documents (Fig. 1a and Fig. 1b. in this section; for an overview of terminology about 'PL-testing' and its varieties see section 1.2).

1.1.1 Basic legal documents

*Council Directive 65/65/EEC of 26 January **1965** on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products* describes in Art 13-20 what information has to be given on the labels of medicinal products.

*Second Council Directive 75/319/EEC of 20 May **1975** on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products* describes in Art 6 and 7 the requirements for PLs. Even though PLs were still not mandatory throughout Europe, the voluntarily created PLs had to be strictly in line with the dossier submitted and had to be approved by the competent authorities (CAs). A list of minimum information was provided in Art 6 however, there was no strict sequence to follow.

[1] Koyuncu A; Pharm R 8:343-348; Der pharmaceutical informed consent - das Modell zur Aufklärung und Information des Patienten vor der Arzneimitteltherapie; 2006

It was explicitly left to the Member States if they would **require** a PL to be included with the packaging.

*Council Directive 92/27/EEC of 31 March **1992** on the labelling of medicinal products for human use and on package leaflets* repealed *CD 65/65/EEC Art 13-20* and *CD 75/319/EEC Art 6 and 7*. As an innovation *Council Directive* (*CD) 92/27/EEC* states in Art 6 for the first time on European level that: '*The inclusion … of a package leaflet … shall be **obligatory**'*. In Art 7 the list of particulars to appear in the PL is extended and a defined sequence is requested.

Additionally, *CD 92/27/EEC* states in Art 8 that *'The package leaflet must be written in clear and understandable terms for the patient and be clearly legible ...'* and in Art 12 that '*As necessary, the Commission shall publish **guidelines** concerning in particular* (amongst others) *the **legibility** of particulars on the labelling and package leaflet.'*
Finally, in Art 12.2, it announces that this guideline (amongst others) '*shall be adopted in the form of a Directive addressed to the Member States …'*

The guideline that emerged, rather late, from these announcements is called: *A guideline on the **readability** of the label and package leaflet on medicinal products for human use* and was approved by the Pharmaceutical Committee in September **1998**. This first European 'Readability Guideline' comprised recommendations for readability and format of labels and PLs. In its Annexes it described a 'model leaflet' and corresponding guidance as well as a method aimed at testing the readability.

As this so-called 'Readability Guideline' was not adopted in the form of a directive, there was no legal enforcement to request PL tests from applicants in form of the '*example of a method for testing the readability of the leaflet'* outlined in its Annex 2.

*Directive 2001/83/EC of the European Parliament and of the Council of 6 November **2001** on the community code relating to medicinal products for human use* repealed CD 92/27/EEC, but did not lead to a change in content. The content of *CD 92/27/EEC* is now covered by Title V Art 54-65 in *Directive 2001/83/EC.*

*Directive 2004/27/EC of the European Parliament and the Council of 31 March **2004** amending Directive 2001/83/EC on the Community code relating to medicinal products for human use* changed the situation within Europe in a quite substantial way as it led to

- the requirement that '*the package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use'* (*Directive 2001/83/EC as amended Art 59 (3)*).
- compulsory submission of '*the results of assessments carried out in cooperation with target patient groups … to the competent authority'* (*Directive 2001/83/EC as amended Art 61 (1) 2nd sentence*).
- harmonised PLs for Mutual Recognition Procedures (MRPs) (*Directive 2001/83/EC as amended Art 28 (2)*) and Decentralised Procedures (DCPs) (*Directive 2001/83/EC as amended Art 28 (3)*), applying also retroactively for MRPs.

Regarding the '*publish'* and '*adoption'* of a detailed guideline '*concerning in particular* (amongst others) *the legibility of particulars on the labelling and package leaflet'* the wording changed from '***As necessary**, the Commission shall ...*' in *CD 92/27/EEC Art 12* towards '*In consultation with the Member States and the parties concerned*, *the Commission **shall** ...*' in *Directive 2001/83/EC Art 65(c) as amended by Directive 2004/27/EC.*

Furthermore, the previously announced adoption in form of a directive was omitted in *Directive 2001/83/EC as amended by Directive 2004/27/EC*. Obviously, as the general request for '*results of assessment*' was implemented by *Directive 2004/27/EC*, it was not considered essential to have the details necessarily nailed down in a directive as well.

In order to adapt the *Readability Guideline of 1998* to pertinent legislation a 'step-by-step approach' was chosen. Two chapters of the future revised Readability Guideline were finalised and published beforehand:

- The *Guidance concerning the Braille requirements for labelling and the package leaflet.* October **2005**, was an amendment and not a revision of the previous Readability Guideline, as it reflects newly implemented obligations.
- The draft *Guidance concerning 'Consultations with target patient groups' for the package leaflet'* was released for comments in August 2005 and finalised in May **2006**.

The complete draft revision of the *Guideline on the readability of the label and package leaflet on medicinal products for human use'* was released for comments in September **2006**.

- This draft revision includes the above mentioned pre-released **Braille guidance** (as chapter 2) as well as the pre-released **Consultation guidance** (as chapter 3).
- Chapter 1 comprises the former 'core guideline' on *Readability of the Label and the Package Leaflet,* 1998.
- As the content of former **Annex 1a** (*An example of a model leaflet*) and **Annex 1b** (*Further Guidance on the content of a model leaflet*) were meanwhile replaced by the Quality Review of Documents (QRD) templates and the annotated QRD template in November 2005 on the European Medicines Agency (EMEA) homepage, these two Annexes have no successor in the current draft revision of September 2006.
- There is only one Annex of the draft revision with an equivalent topic to the former Annex 2 (*An example of a Method for Testing the Readability of the Leaflet*). In the draft revision of September 2006 the respective Annex is called: *ILLUSTRATION – One Way of Undertaking a Test of a Package Leaflet*. However, even if there is resemblance as far as the topic is concerned, the details differ substantially (for details please refer to considerations of pass marks in section 2.2).

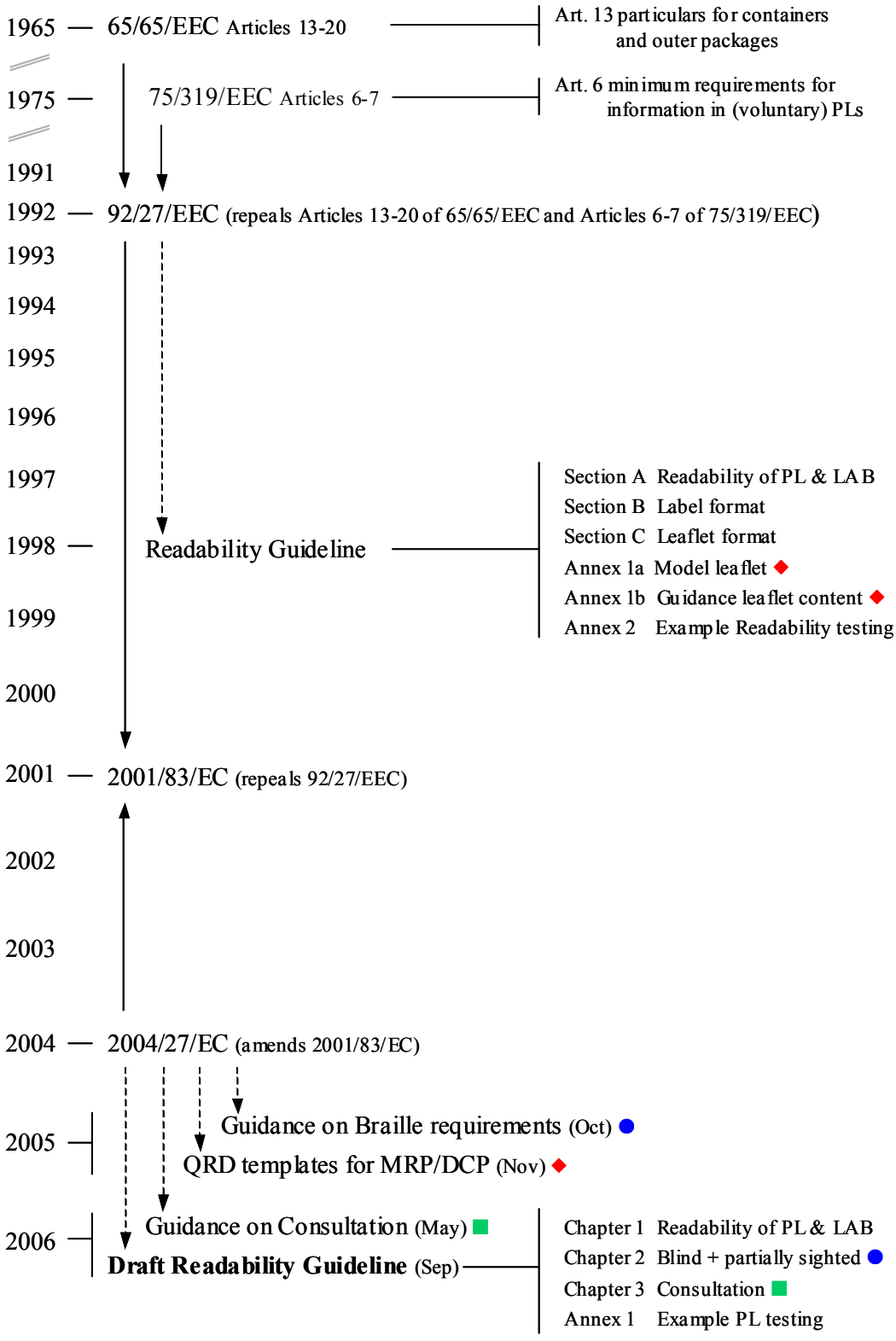

Fig. 1a: Legal roots and legal developments of the European legislation governing the requirements for harmonised PLs and labelling as well as PL-testing. Documents with identically coloured symbols replace each other or derive from each other. Dashed arrows (- - ➔) indicate 'have as consequence the following document'. Solid arrows (→) reflect evolution of pharmaceutical legislation with respect to PL and labelling requirements. DCP: Decentralised Procedure, MRP: Mutual Recognition Procedure, LAB: Labelling, PL: Package Leaflet, for further abbreviations please refer to Appendix 4.

In order to get the complete picture on documents influencing each other or being copied or transferred to other documents in the context of PL-testing, further guidance documents from CAs or institutions are summarised in the following.

1.1.2 EMEA guidance documents for Centralised Procedures

For medicinal products authorised by the Centralised Procedures (CPs) harmonised PLs throughout the Community have been self-evident from the first procedures in 1995. For this purpose, **QRD templates for CPs** were finalised and adopted as early as in 1997[2] and were published on the EMEA homepage in 1998 in an updated version.[3]

Concerning the request for PL-testing there has been a recommendation for it. Accompanying guidance documents were provided by the EMEA, such as:

- *QRD Group Guidance on User Testing of Package Leaflets for Centrally Authorised Products for Human use* (December 1999)
- *Operational procedure on Handling 'Consultation with target patient groups' on Package Leaflets (PL) for Centrally Authorised Products for Human Use* (October 2005)

The first document of 1999 clearly points out the voluntary aspect of performing 'user-testing' and refers to the Readability Guideline of 1998 that stipulates one possible method of a test protocol. It groups the 11 official languages of the European Union (EU) of 1999 into three different linguistic groups and recommends tests in at least one language per group. Finally, it dwells on the timing of 'user-testing' and comes to the overall conclusion that it should be carried out at the latest by Day 121 of the centralised procedure.

The second document of 2005 already takes into account the new medicines legislation (NML, i.e. directives amending *Directive 2001/83/EC*), but it is restricted to mere technical considerations of timing the 'results for user consultation'.

Both guidance documents do not have a direct impact on the current situation for 'established' MRP products. However, the QRD templates for the CPs served as a basis for the creation of the QRD templates for MRP and DCP products in November 2005.

1.1.3 CMD(h) guidance documents to support implementation for NML

Due to the implementation of NML a lot of questions arose, particularly to retroactive application of NML. To support a smooth implementation the 'Coordination group for Mutual recognition and Decentralised procedures – human' (CMD(h)) published as early as in September 2005 '*Questions and answers* (Q&A) *on the implementation of the new medicines legislation'*.[4] There is a section on product information stating in this initial version in Question (Q) 10 that it will not be necessary for products authorised before 30 October 2005 to provide data for PL-testing. However, the accompanying statement that this might be reconsidered if the PL undergoes a 'major change' is considered as a loophole to apply PL-testing retroactively.

[2] EMEA. Third general report 1997 p46 (www.emea.europa.eu/pdfs/general/direct/emeaar/00ar97en.pdf)
[3] EMEA. Fourth general report 1998 p55 (www.emea.europa.eu/pdfs/general/direct/emeaar/ar98en.pdf)
[4] MRFG / CMD(h). Questions and answers (Q&A) on the implementation of the new medicines legislation; September 2005

The Q&A guidance document of the CMD(h) is under ongoing revision, currently at revision No. 6 as of January 2007.[5] In this version the initial Q10 is now Q18, and the revised wording enlarged the loophole a lot.

For specific guidance on how to achieve harmonised PLs the MRFG/CMD(h) set up a *Concept paper – Achieving harmonised Patient information – Patient information leaflets and labelling and the need to take account of patients' view.* This concept paper was finalised in September 2005. Currently, there are no plans to develop this 'concept paper' into a EU guideline, as the procedure for EU guidelines[6] would suggest.

1.1.4 EFPIA documents

In March 2003 the European Federation of Pharmaceutical Industries and Associations (EFPIA) published the revised version of '*General Recommendations for Readability User Testing of Package-Leaflets for Medicinal Products for Human Use Submitted or Approved under the European Centralised Procedure'.* Although PL-testing was not legally obligatory at that time, EFPIA noted that it is strongly encouraged by EMEA and deemed it useful to give its members recommendations. The document concentrates on the method of Diagnostic Leaflet Testing according to the Australian model and its embedding into the regulatory timelines for CPs.

In March 2002 the EFPIA published an Annex to the above-mentioned '*General Recommendations',* which is still the most recent version. This collection of annexes proposes details for various documents, which are needed in the course of performing a Diagnostic Leaflet Test according to the Australian model:

- Annex 1 - Sample protocol. This is currently used as a basis for test protocols by several Contract Research Organisations (CROs). It also serves as guidance for compilation of contracts with CROs.
- Annex 2 - Summary Outcome Report. This is currently reflected in the Draft Readability Guideline / Chapter 3 / 6. Presentation of results.
- Annex 3 - Sample questions. This is currently used by some CROs as a basis for their work.
- Annex 4 - Sample questionnaire. This is currently used by some CROs as a basis for their work.
- Annex 5 - Readability formulae. These are currently regarded as not applicable to fulfil existing legal obligations on their own.

1.1.5 Further documents that influence the content of MRP-PLs

SPC guideline

The first *Guideline on Summary of Product Characteristics* (SPC) was published in October 1991. It was re-issued in 1994 and the first revision was published in 1999. Finally, after six years of discussion, the second revision was finalised in October 2005, which is the current one. The SPC is the basic document for the PL, as the PL has to be '*drawn in accordance*

[5] CMD(h). Questions and answers (Q&A) on the implementation of the new medicines legislation*;* January 2007
[6] EMEA/P/24143/2004 Procedures for European Union Guidelines and related documents within the pharmaceutical legislative framework; 20 June 2005

with the SPC' as first required in *Directive 92/27/EC Art 7*, now covered by Art 59 (1) of *Directive 2001/83/EC as amended*. The SPC Guideline is part of the EudraLex Collection[7] Volume 2C- Regulatory Guidelines.[8]

Excipients Guideline

The *Guideline: Excipients in the label and package leaflet of medicinal products for human use* was first published in July 1997. It later became part of Volume 3B of EudraLex Collection. The first revision was published in July 2003 and is still the current one. This Guideline is based on Art 65 (e) of *Directive 2001/83/EC as amended* and lists for *'those excipients knowledge of which is important for the safe and effective use of the medicinal product'* a wording for the PL. The Excipients Guideline claims that the proposed wording for the PL is '*in clear and understandable terms for the patient*'. With the 'streamline process' of the EudraLex, which took place in 2006, Volume 3B of EudraLex became obsolete and the Excipients Guideline is now available via the EMEA homepage.[9]

Blue Box Concept

The Blue Box Concept for MRP and DCP is the equivalent to the guidance document for the CP *Packaging information of medicinal products for human use authorised by the Community*, June 1997, also called 'Blue Box Guideline', which is currently available in revision 9 as of March 2005. This CP guidance document relates exclusively to the immediate and outer packaging material, it does not relate to PLs.

The term 'Blue Box Concept' relates to decentralised procedures (MRP and DCP) only. It takes into account that there might be a need to have on the national level additional information in the PLs that differ from country to country, even when all national PLs are based on the single PL, which was commonly agreed during MRP. This is reflected in the EudraLex Volume 2A Notice to Applicants (NtA), Chapter 7, section 10 'Blue-box' requirements, stating national texts and requirements for labels and PLs. It was published in May 2006.[10]

The Blue Box Concept triggers quite a lot of discussion, as it is seen as an invitation to deviate from the commonly accepted PL. Astonishingly, this topic seems to be of no relevance for CP products which have managed to cope for 10 years with a harmonised PL throughout Europe without regarding additional text in the PL as being vital for the various countries. In addition, there is little sympathy from pharmaceutical companies as to why the requirements for labels should be different within one country depending on the procedure the medicinal product has gone through.

1.1.6 National documents influencing European guidance and legislation

Guidance documents developed for purely national purposes are also involved in the European context, as they influenced certain documents on European level substantially. Australia and the UK play a major role in this respects. Their influence is symbolised in Fig. 1b. See also section 1.4 *Implementation of PL-testing on national level* for further details.

[7] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm (accessed 10.2.2007)
[8] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm (accessed 7.2.2007)
[9] http://www.emea.europa.eu/pdfs/human/productinfo/3bc7a_200307en.pdf (accessed 7.2.2007)
[10] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/ctd-chap7_2006_05.pdf (accessed 10.2.2007)

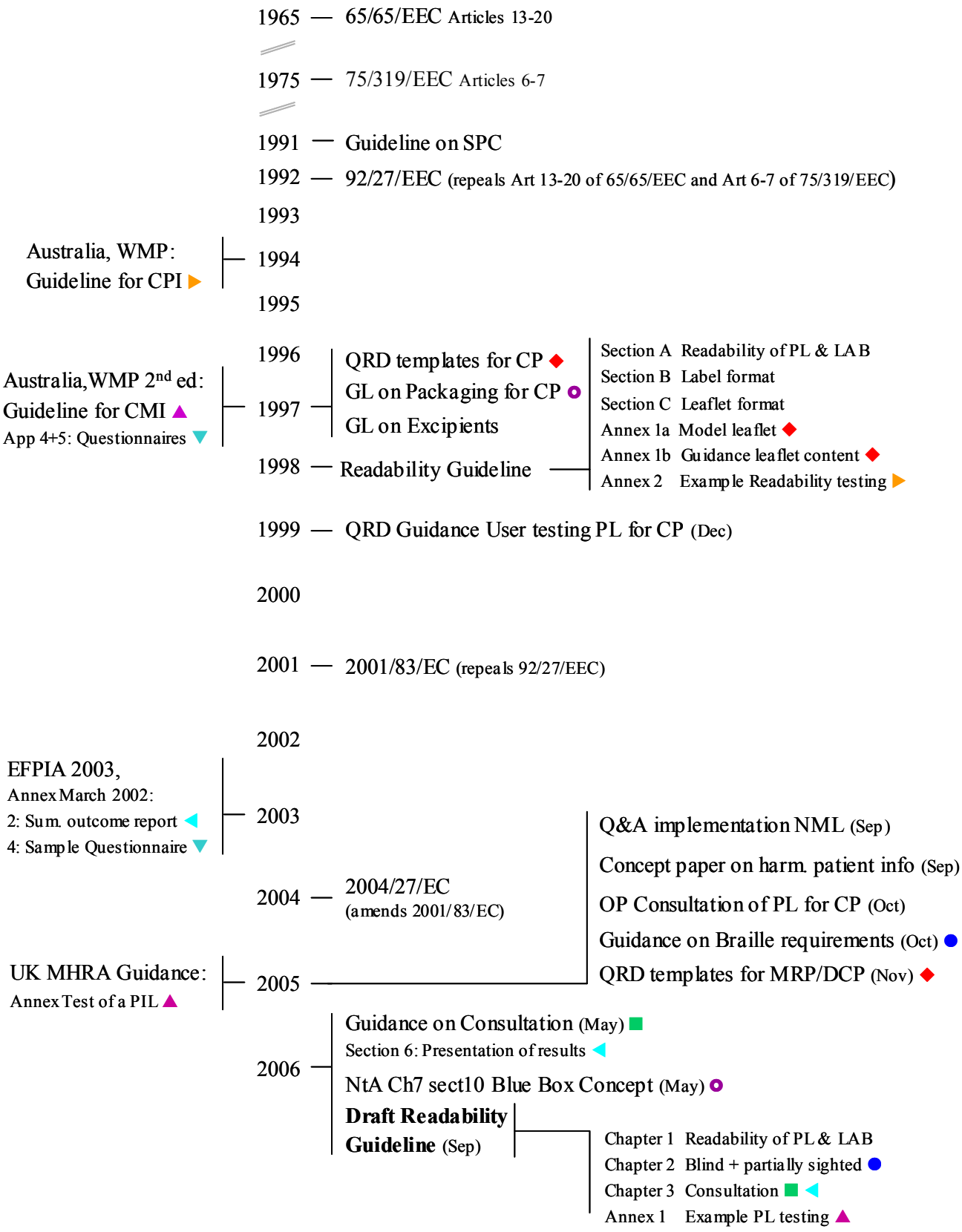

Fig. 1b: Legal roots and legal developments of the European legislation governing the requirements for harmonised PLs and labelling as well as PL-testing with emphasis for MRP relevant documents. Documents with identically coloured symbols replace each other or derive from each other. For UK and Australia related documents please also refer to section 1.4; OP: Operational Procedure, GL: Guideline, CMI Consumer Medicine Information, CPI: Consumer Product Information; for further abbreviations please refer to Appendix 4.

1.2 Terminology – PL-testing and it's varieties

Considering the welter of terminology that is used as a consequence of Art 59 (3) and 61 (1) of *Directive 2001/83/EC as amended*, or has been used earlier with the CPs, it becomes obvious that it is necessary to clearly define the intended meaning of whatever wording is used. In general, there is one group of terms relating to the overarching requirement by legislation and a second group of terms relating to the actual process of how to fulfill the legal requirement.

Terminology used in legislation:

- *'… results of **consultations** with target patient groups'* (*Directive 2001/83/EC as amended* Art 59 (3))
- *'… results of **assessments** carried out in cooperation with target patient groups'* (*Directive 2001/83/EC as amended Art 61 (1) 2nd sentence*)

Terminology used in guidance documents:

- **User testing**. This term is used in the Draft Readability Guideline in Section 3.1 (September 2006).[11] It defines '*User testing means to test the readability of a specimen with a group of selected test subjects.'* It also clearly states that '***One** of the possible ways of complying with the new legal requirement is by performing a 'user testing' of the package leaflet'*. However, the Medicines and Healthcare products Regulatory Agency (MHRA) guidance document (July 2005, see also section 1.4) uses the term in the context of the overall legal requirement as well as for the specific process of 'diagnostic testing' itself.
- **Usability (testing)**. This term is used by David Sless, who heads the former Communication Research Institute of Australia (CRIA), now called CRI. He describes in detail what usability in a broader and a narrower sense means.[12] The latter '… *is concerned with the ease with which people can use labeling'*. His description of the method of how to perform 'usability testing' of PLs is the basis for current EU[13] and MHRA[14] guidances.
- **Diagnostic testing**, iterative. This term is used by Sless to reflect the actual process how usability is tested. A detailed description of iterative, diagnostic testing is described in full length in the *Usability guidelines for CMI* [15] (Appendix 2).
- **User consultation**. According to the introduction of Chapter 3 of the Draft Readability Guideline[11] this term is considered synonymous to *consultations with target patient groups*. In this context the term 'user consultation' is clearly assigned to the overarching requirement of the law. It is <u>not</u> a specific process like e.g. 'user testing'.
- **Patient consultation**. This term appears alternatively to the term 'user consultation' in the Draft Readability Guideline. Particularly the use in the subheading No. 3 (*Forms of patient consultation*) within Chapter 3 makes it evident that the term 'patient

[11] EC. Draft Guideline on the readability of the label and package leaflet of medicinal products for human use; September 2006
[12] Sless D. CRIA. Usable medicines information - Generalised principles and processes for designing usable labels and leaflets for medicine: a review of research and practice 1994-2001; 2001
[13] EC Pharmaceutical Committee; A guideline on the readability of the label and package leaflet of medicinal products for human use; September 1998
[14] MHRA. Guidance on the User testing of patient information leaflet; June 2005
[15] Sless D and Wiseman R. Writing about medicines for people - Usability Guidelines for Consumer Medicine Information. 2nd edition; 1997

consultation' is clearly assigned to the overall legal requirement, as the last sentence of this subsection clearly positions '*user testing'* against '*other appropriate forms of consultation'*.

- **Diagnostic user test**. This term is used in the *CMD(h) concept paper – Achieving harmonised patient information* (point 12), stating that '*... the usual approach suggested* (in the Readability Guideline 1998) *to ensure that the information provided meets patients' needs has been for applicants to undertake a* ***diagnostic user test****'*. Similar to the new Draft Readability Guideline the concept paper clearly states '*diagnostic user testing as being* ***one*** *method of demonstrating compliance with this requirement' (Directive 2001/83/EC as amended Art 59 (3) and Art 61 (1)).*
- **Readability testing**. This term is not actually used in pertinent guidelines or law. It is used very often in an imprecise manner in the regulator's every-day language in the wake of the title of the Readability Guideline of 1998. As a consequence this descriptive term in principle aims to the overarching requirement of the law. However, questioning people what they meant to say by using the term 'Readability testing', often reveals that they thought of the Annex 2 of the Readability Guideline, which describes '*An example of a method for testing the readability of the leaflet'*.[13] In the first paragraph of Annex 2 the described method is explicitly called a 'readability test'.
- **Readability** (according to Sless). This term is often used in relation to medicine labeling. It is sometimes used as synonym for usability (Readability Guideline of 1998).[13] It is also used to refer to legibility: whether or not the font size of a text is large or clear enough to be read.' The term 'readability' in a narrower sense is often used in the context of readability score techniques that count numbers and types of words. The EFPIA Annex[17] describes several readability formulae such as Flesh Reading Ease scale (FRE) and Flesh Kincaid Scale (FK).
- **Readability user testing**. This term is used within the title of the EFPIA guidance documents.[16,17] The document itself deals with the overall legal requirement, but also gives detailed advice on how to perform a diagnostic user test. So, the term 'readability user testing' is commonly understood as the definite process of a diagnostic test rather than the overarching legal requirement.
- **(Leaflet) assessment**. This term, which fortunately is not used in any official guidance document, may refer to *Directive 2001/83/EC as amended* Art 61 (1) '*results of assessment*…' where 'assessment' is used in the context of testing the PL. However, in every day language 'assessment' in any context should be reserved for the work that is done by assessors at the CAs throughout Europe. Furthermore, it should be noted that it is the evaluation of the report on PL-testing that is assessed by the CAs, not the PL itself.
- **PL-testing**. This term was chosen to stipulate the overarching legal requirement as described in *Directive 2001/83/EC as amended* Art 61 (1) within this thesis. This term is not yet fixed by use in any official guideline. Its intuitive associations would be on the one hand to the 'PL' or package leaflet, the term used in **European** legislation, and on the other hand to a very general idea of 'testing'.

[16] EFPIA General Recommendations for Readability User testing of Package leaflets for Medicinal products for human Use Submitted or Approved under the European Centralised Procedure; Rev March 2003

[17] EFPIA Annex to the 'General Recommendations for Readability User testing of Package leaflets for Medicinal products for human Use Submitted or Approved under the European Centralised Procedure'; March 2002

- **Diagnostic Leaflet Testing**. As a consequence of the explanations given above on 'leaflet assessment', particularly due to the fact that it is the PL, which has to be tested, not the user, the specific process of 'diagnostic user testing' would be better understood if it was called 'Diagnostic Leaflet Testing'. Therefore, this term was chosen to stipulate within this thesis one of the specific processes to comply with law for PL-testing.

1.3 Implementation of PLs on national level

Within Europe the requirement to have PLs that accompany the medicinal products was developed in the EU countries at different times and with diverse speed (Tab. 1 *Overview of the requirement for PLs on national level).* In many EU countries national regulations on PLs were already in place, when *Directives 75/319/EEC* or *92/27/EEC* came into force. These countries had to adapt their national regulations to be in line with the EU requirements. Particularly the content and order of PL items had to be adapted, as well as the addressee, i.e. the patient. In the course of implementing *Directive 92/27/EEC*, which made PLs mandatory, some countries even had to adapt their distribution system to conform with the generally accepted mode of 'original drug dispensing'. In NL, DK, IE and UK, for example, community pharmacists repacked a substantial part of the medication volume at that time, whereas most of southern Europe, BE, and DE distributed pharmaceuticals in branded packages.[18]

A prerequisite for countries joining the EU is acceptance and implementation of the *aquis communitaire*. Therefore, all countries that joined the EU after 1992 should have PLs according to EU guidelines at least since date of EU accession. However, for quite a few countries joining the EU (or EEA) was the trigger for first-time implementation of PLs in their countries (e.g. FI, SE, MT).

Tab 1: A simplified overview of the requirement for **PLs** on national level in countries that are currently in the EU or EEA. The left column shows countries (according to ISO code 3166) listed according to the year of accession. The centre column states the year (if available) of the first legislation that made PLs mandatory, as well as additional circumstances (if known). The right column lists the sources of information. This information has to be used with caution as it was not possible for the author to find, access and understand all country-specific original national laws.

Country	Requirement for PLs on national level	Source
BE **1951**	**1977** PLs are usual but not compulsory. For new MAs a draft PL is required. **1969** Royal Order of 03 July on registration of medicinal products describes 'leaflet containing information for the user which accompanies the medicinal product'. **1986** All new product applications must include a package insert. Transition time for established products is 2 years.	Whittet[21] Pers. comm.[19] (10.11.2006)
DE 1951	**1976** Drug Law makes PLs mandatory, but they need not be patient oriented. Introduction of a separate data sheet for the physician in **1986** created the opportunity to address the package insert solely to the patient.	AMG BGBl I p2445-8, 24 August 1976 2.ÄG AMG BGBl I p 1296, 16 August 1986
FR 1951	**1977**: PLs are not mandatory, but possible when they are approved by CA. **1987** It is compulsory to provide patients with information. **1994** Implementation of *Directive 92/27/EEC* via Decret 94-19 of 5 January 1994	Whittet[21] ABPI[20] Pers. comm.[19] (29.11.2006)

[18] Stichele vd R, Bogaert MG, Drug Inf J 29:285-290. European legislation and research projects regarding patient education for medication; 1995
[19] Personal communication. This information was retrieved at various occasions on a company-internal basis.
[20] ABPI The Association of the British Pharmaceutical Industry. Information to patients on medicines; 1987

IT 1951	**1977** PLs are used, but not compulsory, they must be approved by CA. **1992** Since decree 540 of 30 December, the first structured requirement for PLs exists, theoretically addressed to the patient. In reality a 1:1 copy of relevant SPC-sections is used in the PL. **2006** PLs are in line with EU-guideline since decree 219 was published June 21.	Whittet[21] Bernardini[79] Pers. comm.[19] (15.1.2007)
LU 1951	*No information available. Might have developed parallel to DE*	
NL 1951	**1977** It is compulsory to supply package insert leaflets when the prescription is for the 'original' package. **1988** PLs are used on a voluntary basis. However, the scientific leaflet (for physicians) often was in the package. **1994** Official Dutch guideline is published on 29 June. It makes PLs addressed to the patient mandatory in the package.	Whittet[21] Pers. comm.[19] (17.11.2006)
DK **1973**	**1993** With Ministerial order no. 314 dated 18 May PLs were implemented in DK. There was an interim period for implementation.	Pers. comm.[19] (17.1.2007)
IE 1973	**1994** Implementation of *Directive 92/27/EEC*: Medicinal preparations Regulations 1993 S.I. No 71 1993 required a PL for any products authorised after 1 January **1994**. **1996** All existing authorisations must also comply with that regulation.	Pers. comm.[19] (16.11.2006)
UK 1973	**1994** The Medicines Act 1968 (Amendment No. 2) Regulation 1994 No. 276 introduced the requirement that all marketing authorisations (or renewals) issued after 13 February 1994 comply with the labeling *Directive 92/27/EEC*. As a result in February **1999** all medicinal products should be provided with a PL	Pers. comm.[19] (16.11.2006)
1975	*Second Council Directive 75/319/EEC of 20 May 1975*	
GR **1981**	**1987** Patient package Inserts (PPIs) are produced for the combined use of patients and physicians. **1993** Implementation of *Directive 92/27/EEC* in Ministerial Decree Y6a/776/93	ABPI[20] Pers. comm.[19]
ES **1986**	**1977** It is compulsory to supply package insert leaflets at least since 1977.	Whittet[21]
PT 1986	**1957** PLs were legislated under Decree Law 414488 dated 18 December PLs were directed to the patient from the start.	Pers. comm.[19] (8.11.2006)
1992	*Council Directive 92/27/EEC of 31 March 1992*	
IS EEA **1994**	**1995** PLs became mandatory.	E-mail CA Iceland (Thorbjorg Kjartansdottir) 8.1.2007
NO EEA 1994	**1994** PLs became legally mandatory in Norway, when *Directive 92/27/EEC* was implemented. *Directive 92/27/EEC* was made a part of the EEA agreement by the EEA joint committee decision of 21 March 1994, that came into force 1 July 1994	E-mail CA NO (Catrine Hodnesdal Karlöf) 17.1.2007
AT **1995**	**1977** PLs are usually included with all pharmaceutical specialities. The PL is directed to the patient as well as to the physician. **1983** PLs are mandatory for all medicinal products. PLs must be directed to the patient. The current legal basis for PLs is laid down in paragraph 8 to 9a of the Austrian Drug Law.	Whittet[21] Pers. comm.[19] (10.11.2006)
FI 1995	**1995** When FI joined the EU (1 January **1995**) PLs became mandatory for new applications. It took over 5 years (until 2000) before PLs were approved for all products. PLs were directed to patients right from the start.	Pers. comm.[19] (7.11.2006) Admin Regulation No. 5/2005
SE 1995	**1995** With entrance to the EU PLs became mandatory. PLs for medicines administered by Health care professionals (HCPs) became mandatory only after introduction of NML (30 October 2005).	E-mail CA SE (Christina Wik) 10.1.2007
CY **2004**	**1967** Leaflets became mandatory. The PLs were directed both to patients and physicians, but there was no requirement to use the Greek language.	E-mail CA CY (MoH Sofia Petridou) 21.2.2007

[21] Whittet TD, Drug Inf J 26S-34S. The viewpoint of the European Experience; 1977

CZ 2004	**1926** PLs became mandatory according to Government regulation concerning the manufacture of medicinal specialities and their sale in pharmacies. The current legislation covers PLs in Act No. 79/1997 Coll. on Pharmaceuticals as amended, and Decree 288/2004.	E-mail CA CZ (SUKL, Tereza Stepankova) 21.1.2007
EE 2004	**1996** PLs became mandatory.	E-mail CA EE (Maia Uusküla) 8.1.2007
HU 2004	**1930** PLs are mandatory from the beginning of registration of medicinal products in HU. The addressee of the first leaflets was the physician. **2004** *Directive 92/27/EEC* is implemented via *Directive 2001/83/EC* which was implemented in Act XXV/1998 amended by Act XXVI/2004.	Pers. comm.[19] (24.1.2007)
LT 2004	**2001** Decree No. 308 of 29 May implemented the *Directive 92/27/EEC* The current version of Jan 09, 2005 is line with *Directive 2001/83/EC* and *Directive 2004/27/EC.*	www.vvkt.lt
LV 2004	**2003** A new law came into force on 29 March, describing the PL requirements basically according to EU-requirements. **2005** A guidance document from 26 May introduced the common Baltic PLs that are in line with QRD templates.	www.zva.gov.lv
MT 2004	**2004** Since EU accession in 2004 PLs are mandatory. As most medicines on the market were already authorised in other EU countries they had a package leaflet anyway.	E-mail CA MT (MHEC, Hellen Vella) 9.1.2007
PL 2004	**1977** 'Information about the medicine' is not mandatory, but must have government approval, when used. PLs are supplied most often with newly marketed medicinal products. It was directed to physician and patient as well. **2002** Decree 02.234.1978 was published on 19 December 2002. It came into force on 1 January 2003 and made PL requirements mandatory according to EU standard. Now PLs address the patients.	Whittet[21] Pers. comm.[19] (15.2.2006) J. of Laws 02.234.1978
SI 2004	**1980's** 'Instructions' are mandatory to accompany medicinal products. They addressed both, the physician and the patient, at the same time. **1999** A new regulation was issued 16 December 1999. This resulted in rules for PLs and Labelling, issued 20 September 2000. From then on separate SPC and PL were created.	Pers. comm.[19] (17.1.2007)
SK 2004	**1995** A Slovak version of PIL is strictly demanded (according to the law on official Slovak language). **1998** PLs in compliance with EU standard have become legally mandatory in Slovakia (Act 140/1998 on medicinal products and medical devices came into force).	E-mail CA SK (SUKL, Dr. D Vyskocilova) 18.1.2007
BG **2007**	**1904** Birth date of medicinal regulation in BG on 31 October (Decree 44 of royal prince Ferdinand by virtue of art. 169 of the Public Healthcare Protection act).	Pers. comm.[19] (5.2.2007)
RO 2007	**1900** (approx.) Leaflets accompany medicinal products from beginning of pharmaceutical industry in Romania. **1999** (approx) SPCs and PLs are mandatory for all products on the market.	Pers. comm.[19] (9.2.2007)

1.4 Implementation of PL-testing on national level

<u>Outside Europe – where it originated</u>

Australia

From the European perspective the foundation of PL-testing is in Australia. A fundamental work was done by Sless from the Australian CRI(A). In 1994 Sless and Wiseman published *Writing about Medicines for people: Usability Guidelines for Consumer Product*

Information,[22] called 'WMP'. This guidance document was based on studies performed of five existing medicine leaflets. This first edition of WMP formed the basis for the European authorities when they developed the Readability Guideline in 1998, particularly Annex 2. In Australia the Consumer Medicine Information (CMI) itself became only mandatory in 1993 for new Marketing Authorisation Applications (MAAs) ('*prescription only medicines'*) and for variations on MAs issued before 1993.

In 1997 CRIA was commissioned to write a second edition of 'WMP' incorporating the experience of applying WMP that was gained within the pharmaceutical industry for approximately 700 products. The 2nd edition took also into account that in April 1997 the name changed from 'Consumer Product Information' towards 'Consumer Medicines Information'. Therefore, the title was as follows: *Writing about Medicines for People: Usability Guidelines for Consumer Medicines Information, 2nd edition 1997.*[15]

Part of this new edition is a detailed description of how to perform a diagnostic test on the leaflet in order to ensure that it is understood by the patient, enabling him/her to act appropriately in various situations. However, even when CMI is required to be written according to WMP, there is **no need to submit results of diagnostic testing of the leaflets** to the Therapeutic Goods Authority (TGA). In Australia CMI is only submitted and approved for the initial MA. Afterwards, all Physician's Information (PI) changes that need to be approved by TGA are expected to be reflected accurately in the CMI as well. There is no CMI approval during the lifecycle of a medicinal product.

Europe

Within Europe the requirement to test PLs of medicinal products developed in the various countries at different time and speed. However, in all European countries this requirement was only triggered by *Directive 2004/27/EC* and its transition period until 30 October 2005. The majority of countries within the European Community (EC) or European Free Trade Association (EFTA) did not require PL-testing on a mandatory basis before the transition period ended; exceptions being the UK and DE. Here, the PL-testing requirement was implemented for new MAAs four months or three weeks, respectively, before the transition period expired. In Tab. 2 (below) a rough overview of the situation in the respective countries is given.

UK

The MHRA developed a national guideline called *Guidance on the User testing of patient information leaflet,* which became effective on 1 July 2005.[14] Obviously, the second edition of the Australian WMP was used as a basis to create the Annex of this Guidance document. This Annex of the UK guidance was transferred verbatim to the Annex of the European Draft Readability Guideline published in September 2006. The only change from the original UK guidance document was the replacement of the term 'PIL' ('patient information leaflet') by the term 'PL' ('package leaflet'). So far, the UK is the only country within the EU that explicitly requires all existing PLs to be tested retroactively or to justify non-testing by bridging[23] to other tests. Timelines are tight, as the deadline is July 2008, and consequently MHRA asked MAHs to provide tests and justifications by the end of 2007. Around 10,000 submissions are awaited.[24]

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[22] Sless D, Wiseman R. Canberra: Department of Health and Human Services. Writing about medicines for people. Usability Guidelines for Consumer Product Information; 1994

[23] MHRA. Guidance for the Pharmaceutical Industry on the use of BRIDGING STUDIES to demonstrate compliance with Art 59 (3) of *Council Directive 2001/83/EC* [Consultation with Target Patient Groups]; December 2006

[24] Harrison F. Topra. Meeting reports TOPRA North of England workshop Readability testing; September 2006

DE
DE also implemented *Directive 2004/27/EC* before the end of transition period. However, in contrast to the UK the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) did not command for submission of PL-testing reports for all 'established' products within a preset time frame. There is a request in the national law, the Arzneimittelgesetz (AMG), that all PLs have to comply with § 10 (Labelling) and § 11 (PL) at latest by 1 January 2009. The PL-testing report is not explicitly part of § 11, but it is mentioned in § 22 (7). Nevertheless the German CA strongly recommends to perform PL tests on established products (Tab. 2).

BE, HU, IE, FR
Several EU countries implemented the requirement for PL-testing with delay and require that after a certain transition time **all** existing PLs have to comply with the new requirement in form of reflecting actual PL-testing. HU and IE, for example; ask for the year 2010 as end of national fulfilment. BE asks for the year 2013 and FR plans to have a transition period over 3 years (Tab. 2).

AT, DK, IT, PL
Several EU countries implemented the requirement for PL-testing with delay, but did not explicitly define to which MAs this new obligation applies (Tab. 2).

CY, EE, GR, LT, NO, SK
Some countries either forgot to mention the PL-testing in their law (NO, SK), or have major delay in the implementation of NML itself (Tab. 2).

Tab. 2: A simplified overview of the requirement for **PL-testing** at the national level in countries that are currently part of the EU or EEA. The left column lists countries (according to ISO code 3166) in alphabetical order. The centre column states the date (if available) of first legalisation that made PL-testing mandatory, as well as additional circumstances (if known). The right column shows sources of information. The information and data has to be used with caution as it was not possible for the author to find, access and understand all country-specific original national laws.

Country	Requirement for PL-testing at the National Level	Source
AT	**2006 Jan 02** Mandatory for new MAs as of 2 January 2006. MAs dated before implementation: PLs have to be tested with major variations of relevant parts (warnings, indications).	EFPIA comm. (January 2007)
BE	**2007 Jan 01** Enforced. MAs valid prior to enforcement will have to comply within 5 years after 1 January 2007 (i.e. 2013) on occasion of renewal or variation. In case of significant change of PL-testing is mandatory. One language will be sufficient for testing.	Pers. Comm.[19] (Official languages in BE: fr, de, nl)
BG	Not yet implemented. New Draft legislation is under preparation.	Pers. comm.[19]
CY	Not yet implemented.	EFPIA comm. (January 2007)
CZ	Implemented in Draft regulation.	Pers. comm.[19]
DE	**2005 Sep 06** Mandatory for all new MAAs. No requirement for MAs authorised before 6 September 2006, but strongly recommended.	EFPIA □omm.. (January 2007)
DK	Mandatory. Testing must not necessarily be on Danish PL version, but summary of test results has to be submitted in Danish.	EFPIA □omm.. (January 2007)
EE	Mandatory for new MAAs from the day the decree comes into force (expected for 2006, but still outstanding as of the time this thesis is being written.) MAs prior to 30 October 2005 will have to comply at the next renewal	EFPIA □omm.. (January 2007)
ES	Only a general statement in the draft of the new law. 'The leaflet has to assure its comprehension by the patient'.	Pers. comm.[19]

FI	**2005 Oct 30** Mandatory for all applications (MAA, renewals, variations). One language is sufficient. With FI being reference member state (RMS) testing is required in Finnish or Swedish. In practice: not required for national MAs during variation or renewal.	EFPIA □omm.. (Official languages in FI: fi, sv)
FR	Not yet implemented as of Dec 2006, but has to be taken into account. Will be mandatory for all new MAAs from date of the law coming into force. A three year transition period for existing MAs is expected.	EFPIA comm. (January 2007)
GR	**2006 Jan 24** Mandatory. Ministerial decree issued in January 2006. Not specified, what 'Consultation with target patient group' means, no guidelines.	Pers. comm.[19]
HU	**2005 Oct 30** Mandatory for new products. Until 31 December 2010 all PLs must comply.	Pers. comm.[19]
IE	**2005 Oct 30** Mandatory for MRP and DCP. Mandatory for national MAA since decree came into force. PL test for old leaflets required by 2010.	EFPIA comm. (January 2007)
IT	**2006 Apr 24** Mandatory. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use (Legislative Decree n° 219 of April 24, 2006, Art 77, sub 4).	IDRAC, Explanatroy Information / Italy July 2006
LT	Implementation rules still missing.	EFPIA comm. (January 2007)
LU	*Not available.*	
LV	Mandatory. Already marketed product must comply with this requirement until 30 October 2008.	Pers. comm.[19]
MT	Mandatory. As UK packs are often shared, PL-testing performed in the UK is likely to be accepted.	EFPIA comm. (January 2007)
NL	Not yet implemented, but Medicines Evaluation Board (MEB) acts as if implementation is a fact.	Pers. comm..[19]
NO	Not foreseen in draft regulation.	EFPIA comm. (January 2007)
PL	Mandatory.	EFPIA comm. (January 2007)
PT	**2006 Dec** Mandatory. Transposition of EU-Law via Law n°176/2006 (Dec)	Pers. comm.[19]
RO	Not yet implemented.	Pers. comm.[19]
SE	**2005 Oct 30** Mandatory for new MAAs and for MR products. For MAs before 30 October 2005 recommended in case of significant changes; all product have to comply at latest 5 years after approval with NML.	EFPIA comm. (January 2007). Pers. comm.[19]
SI	Mandatory. Any language permitted. No request for purely national PLs.	EFPIA comm. (January 2007)
SK	Not yet implemented in the new Slovakian Law that is effective since 1 June 2006.	Pers. comm.[19]
UK	**2005 Jul 01** Mandatory for new MAAs. All PLs of all MAs must reflect PL-testing by July 2008.	EFPIA comm. (January 2007)

Different implementation timelines at the national level can potentially cause inconsistent approaches during MRP. Therefore, Member States expressed their willingness to adhere to the NML regardless of the implementation status in their individual country:

'It is the legal responsibility of the Member States to comply with the requirements. Not withstanding any individual Member State's position regarding transposition of the Directive, ***all Member States have agreed to follow the new procedures in practice from this date'*** (Sept 2005).[4]

2 PL-testing in relation to the overall business process

Implementing new processes into established structures of a pharmaceutical company

Any pharmaceutical company that wishes to be active in the global or at least the European marketplace needs to deal with the legal obligations concerning PL-testing. It must recognise and provide for the new responsibilities under these new requirements. This goes along with the requirement to have a harmonised EU PL for MR countries and the bonus to have this harmonised EU PL tested only in one of the European languages.

Before the NML came into force the national PLs for MRP products were purely national affairs. Therefore, most pharmaceutical companies dealt with it via their local affiliates or agents, as they were the experts in the individual national requirements for the respective national PLs. However, there now is the need for one common PL that matches all national requirements of the Concerned Member States (CMS) involved and to have this PL tested for usability. In the search for a 'home' for this new responsibility common sense points directly to the unit within the company, which deals with the SPCs for the MRPs. This is in general the headquarters (HQ) of the company.

When transferring the responsibility to write the PL for MRP products from the local level to the HQ, the following aspects have to be considered:

- Although all PLs written within the past years in the EU should be based on the common '*Directive 92/27/EEC* principles', national use and implementation varies a lot. The **know-how of 'national specialities'** rests with the local level and has to be made available to the HQ.
- The local level has to be made aware of the new process. Implementation of *Directive 2004/27/EC* was not fully achieved by 30 October 2005 in all EU countries. Therefore, in some countries affiliates may have to be informed about applicability although a national law may be missing.
- The **interaction** between local affiliates and HQ has to be increased for the development of a common PL that provides the optimum fit for all involved countries.
- Timely transmission of documents and information has to be ensured between local affiliates and HQ. As always when introducing new processes within a company the guarantee for success is early and open **communication** between all partners involved.

Within the HQ, several changes are necessary in order to succeed:

- **New resources** for personnel and budget have to be approved.
- Assignment of new **responsibilities** has to be considered, e.g. choosing between task-related and product-related approaches.
- New **skills for writing PLs** have to be acquired. This is particularly important for companies that have no or little CP products and relied in general on their affiliates for the various national PLs.
- Concerned units (clinical, pharmacovigilance, commercial, regulatory affairs) have to be made aware of the new process and the extent of input required from them.
- Various approaches for fulfilment of the legal requirements of PL-testing have to be considered. The **decision** to select a specific **PL-testing procedure** has to be taken.
- A decision has to be made whether the PL-testing procedure is a process which will be established within the company or if parts or the whole process will be outsourced to a Contract Research Organisation (CRO).

- HQ has to consider how to 'fit in' additional regulatory procedures with the timing for other necessary regulatory procedures.
- The current 'house-style' of the company's existing **PL design** has to re-thought.

The following subsections will discuss the issues outlined above in a structured manner:

Subsection 2.1 gives an **overview of test methods**. Patient information was tested long before *Directive 2004/27/EC* for various reasons. Therefore several tests evolved, whose names confuse the current terminology on PL-testing. This thesis displays a **broad range of test methods**, even when not all of them are 'usable' for the purpose of meeting current legal obligations. The aim was to facilitate the understanding of the differences and to clearly define them.

Subsection 2.2 deals with **Diagnostic Leaflet Testing** as one specific method to test readability of a PL. This method meets current legal obligations, is widely acknowledged by CAs, and is used in many pharmaceutical companies. The development of standards for success under this method and its guidance documents is discussed.

Subsection 2.3 addresses the issue of **CROs,** which evolved to perform Diagnostic Leaflet Testing for pharmaceutical companies.

Subsections 2.4 and **2.5** tackle **money and time** respectively. Both are essential issues for pharmaceutical companies.

Subsection 2.6 focuses on time with respect to the **regulatory aspect** of the various **procedures** (CP, DCP, MRP, national). MR procedures are emphasised.

Subsection 2.7 considers **technical** aspects that arise through harmonised PLs, including different languages and specific national requirements. In practice these aspects challenge established procedures in the companies.

2.1 Overview of test methods

A vast amount of acronyms and catchwords for testing methods emerge when starting to search for testing methods using keywords such as 'leaflet', 'patient', 'readability', or 'testing'. Sorting the retrieved items vis-à-vis the different levels of the reading process helps to gain an overview of the purpose and usability of the various methods (Fig. 2).

Testing methods can be grouped considering the tested, physical **object** (patient or package leaflet), the **type of person** involved, if any (patient or Health Care Professional (HCP)), and the **purpose** the test aims at (readability, literal comprehension, understanding, or ability to act upon).

The four main resulting groups are:

- Readability formulae / Readability instruments
- Health literacy tests
- Design assessment tools
- Direct patient-PL interaction test

These groups are outlined in the following subsections (see also Fig. 2). Further test details are described in Appendix 2.

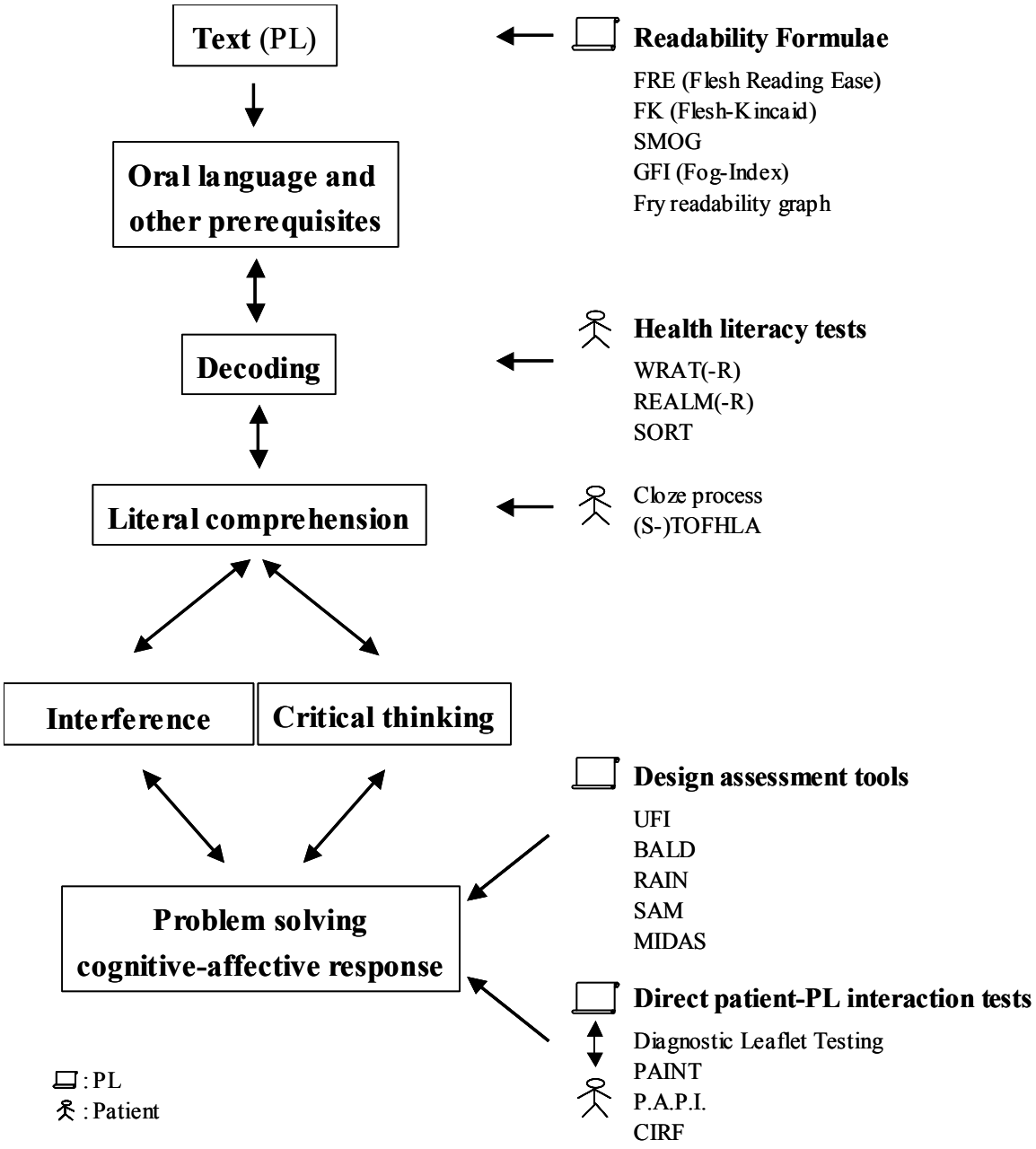

Fig. 2: Overview of various test methods for 'Readability'. The methods were grouped into four main sections: 'Readability Formulae', 'Health literacy tests', 'Design assessment tools', and 'Direct patient-PL interaction tests'. Sorting the tests (or its acronyms) vis-à-vis the levels of the reading process (Source: Tutor, Literacy Volunteers of America Inc., Syracuse, NY) helps to gain an overview of purpose and usability for fulfilling the legal obligations of *Directive 2004/27/EC*. Specific details about the tests are described in Appendix 2.

2.1.1 Readability Formulae / Readability instruments

Readability Formulae were initially developed as an assessment tool for teachers at schools when choosing literature for pupils in different grades. They are predictive devices that provide quantitative estimates of the reading difficulty of printed (health) information by determining the complexity of vocabulary used and the length of sentences. Application of these two factors in a readability formula provides a grade-level rating. This presents the average reading skills achieved in each year of schooling in the American public school system.

One must be very aware of the fact that these Readability Formulae do not take into account the readers' prior knowledge, motivation, or comprehension.[25] A major feature of these formulae is that the result would be the same, if the words within a sentence were ordered in a different, 'incomprehensible' way, such as 'end the from sentence a starting'. The formulae are applicable to the text body (prose text) of the PL to be tested, but can not be applied to tables, charts, or word lists within a PL. There is no patient or health care professional directly involved in the test. There are more than 40 different formulae that can be used to perform a readability test. Only the five most frequently mentioned formulae in the context of health literature are shown in Fig. 2 and described in Appendix 2. Amongst these there are also those three formulae mentioned in the EFPIA Annex[17] (i.e. the **Flesh Reading Ease Scale**[26] (FRE), the **Flesh-Kincaid scale**[27] (FK) and the **Simplified Measure Of Gobbledegook**[28] (SMOG)). The EFPIA Annex points out that the Readability Formulae have their limitations in assessing the usability of PLs. It recommends a 'combined approach', where the application of a Readability Formula is only one part of a set of complementing test procedures.

⇒ Due to the obvious shortcomings and limitations of **Readability Formulae**, they do **not** present an option to be chosen to fulfil the legal obligations of PL-testing as required in *Directive 2004/27/EC*.

2.1.2 Health literacy tests

This group of tests is quite heterogeneous and comprises tests also known as **word-recognition tests** such as the Wide Range Achievement Test-Revised[29] (WRAT-R) or Rapid Estimate of Adult Literacy in Medicine[30](-Revised)[31] (REALM (-R)), but it also covers so called **comprehension instruments** such as the Cloze procedure[32] or the (Short) [33] Test Of Functional Health Literacy in Adults[34] ((S-)TOFHLA). Their commonality is that it is the person's health literacy that is being assessed, not the PL itself. In most of the tests the PL is not even involved in the entire test procedure.

Word-recognition tests use predefined lists of words and evaluate the tested persons' ability to read and pronounce the words sorted by increasing demands. They relate to the pure decoding step within the reading process and do not allow any conclusion on the level of comprehension or even the ability to react in a proper way. They are in no way connected to the PL to be tested and therefore are not considered in this context any longer.

The **comprehension instruments** Cloze procedure or TOFHLA are based on a technique which replaces in a text every n^{th} (e.g. 5^{th}) word by a blank and lets the tested person fill in the gaps (Cloze) or select the correct replacement from a choice of four (TOFHLA).
The TOFHLA test consists of three predefined text passages. Their topics are the preparation for an upper gastrointestinal series, a patient's right and responsibilities section of a Medicaid

[25] Bailin A, Grafstein A. Language and Communication 21:285-301. The linguistic assumptions underlying readability formulae: A critique; 2001
[26] Flesh R. Journal of Applied Psychology 32:221-233. A new readability yardstick; 1948
[27] Kincaid JP, Fishburne RP, Rogers RL, Chissom BS: Milington, TN. Navy Research Branch. Derivation of new readability formula for navy enlisted personnel; 1975
[28] McLaughlin GH. Journal of Reading, 12: 639-646. SMOG grading - A new readability formula; 1969
[29] Jastak S, Wilkinson GS, Wilmington DE. Jastack Associates. Wide range achievement test-revised; 1987
[30] Davies TC, Crouch MA, Long SW, Jackson RH, Bates P, George RB. Family Medicine 23:433-435. Rapid assessment of literacy levels of adult primary care patients; 1991
[31] Bass PF, Wilson JF, Griffith CH. J. Gen Int Med 16:117. A shortened instrument for literacy screening; 2001
[32] Taylor WL. Journalism Quarterly 30:415-433. 'Cloze procedure': A new tool for measuring readability; 1953
[33] Baker DW, Williams MV, Parker RM, Gazmararian JA, Nurss J. Pat Ed Couns 38:33-42. Development of a brief test to measure functional health literacy; 1999
[34] Parker RM, Baker DW, Williams MV, Nurss JR. J Gen Intern Med. 10:537-41: The Test of Functional Health Literacy in Adults: a new instrument for measuring patients' literacy skills; 1995

application, and a standard hospital consent form. Therefore, it is always the same basis on which the people's health literacy is assessed. In this form, the TOFHLA test is not relevant to the PL to be tested and therefore is not considered in this context any longer.
In contrast, for the Cloze procedure any text can be chosen, including a PL to be tested. However, the resulting scores have to be seen in correlation with two variables:

- Degree of health literacy of the people tested
- Degree of complexity of the underlying test text of the PL

Pertinent literature[35] still considers a score of more than 75 % as showing adequate health literacy, i.e. comprehension, by the patient. However, there are no data available for the validity of this score by proving that the respective PLs are *legible, clear and easy to use* as required by law.

⇒ Due to the different test objects in **health literacy tests** (i.e. the patient, not the PL) these methods, as currently applied, are of **no use** for fulfilling the legal obligations of PL-testing as in *Directive 2004/27/EC*.

2.1.3 Design assessment tools

This group of tests contributes to the insight that there are factors beyond the mere scientific facts that make a PL understandable or easy to act upon. Guidelines to facilitate the presentation of well designed information for patients on medicinal products were initiated by the U.S.,[36] European,[13,11] and Australian[22,15] governments. Furthermore, individual research groups developed guidance on features of well presented written 'Drug Information'. A summary is shown in Tab. 3.

Tab. 3: A summary of the favourable design features according to Koo et al.[37] This compilation is based on the scientific work of several groups of researchers.[38, 39, 40, 42, 45, 46]

Characteristics	**Desirable Features**
Font	Typeface: Serif Style: No italics, bold for emphasis, mix of upper and lower case letters Size: 10 point (12 point for older persons)
Numerals	Arabic rather than Roman
Colour	Increase appeal and enhance text, without distracting from it
Illustrations	Use only if relevant and amount of text can be saved (e.g. application of eye drops).
Paper	Colour: Good contrast between text and paper Quality: 75-90 g/m^2
Format	Bullets: Use encouraged Heading: Clear and outstanding with a mix of upper and lower case letters Justification: Justified on left but not on right Line length: 30-50 characters and spaces Paragraph: Indent first line White space: Ample (i.e. leaflet should not appear over-crowded with text)

[35] Mancuso CA, Rincon MR. J Gen Intern Med 21:813-817. Impact of health literacy on longitudinal asthma outcomes; 2006
[36] FDA Guidance Useful written Consumer Medication (CMI); July 2006
[37] Koo MM, Krass I, Aslani P. The Annals of Pharmacotherapy 37:259-267. Factors influencing Consumer Use of Written Drug Information; 2003
[38] Bandesha G, Raynor DK, Teale C. Int Pharm Pract 4:246-8. Preliminary investigation of patient information leaflets as package inserts; 1996
[39] Kitching JB. J R Soc Med 83:298-300. Patient information leaflets – the state of the art; 1990
[40] Raynor DK. Pharm J 249:180-182. Writing patient information – a pharmacists guide; 1992

Several instruments have been developed to evaluate the design characteristics of written information of medicinal products. They mainly exist in the form of check-lists, some of which yield scores for (partial) fulfilment. Examples for these instruments are:

- User Friendliness Index[41] (UFI)
- Baker Able Leaflet Design[42] (BALD)
- Readability Assessment Instrument[43] (RAIN)

Two further design assessment tools claim to be validated/verified[44] by consumer testing, a point of major importance when considering the probability of acceptance by European CAs:

- Suitability Assessment of Material[45] (SAM)
- Medication Information Design Assessment Scale[46] (MIDAS)

For all methods mentioned and with other design assessment tools as well, the evaluation of the particular PL is done without the target client group. This fact itself is not a general hindrance for acceptance by European CAs. However, there needs to be a sound data package to validate/verify[44] the design assessment technique. Such data have to be developed first by consultation with target patient groups and then validated/verified by showing that the results of this technique are reliable and repeatable. These results should prove that patients are able to read, understand, and properly act upon the tested PL.

Unfortunately, both 'user validations' for SAM and MIDAS were done for purposes other than fulfilling requirements of European laws. Currently, there is no 'ready to use' design assessment tool available in a similar way as the Diagnostic Leaflet Testing (section 2.1.4.1).

However, at least one known system, developed independently from the pharmaceutical business and its regulations, is currently applied to various sorts of texts. It is not yet 'verified' to fulfil the legal obligations, but it could be a starting point for a new 'ready to use' technique:

Crystal Mark

In the UK the Plain English Campaign in 1990 introduced their seal of approval - the Crystal Mark - to encourage organisations to clearly communicate with the public.[47] There is an astonishing resemblance to the PL-testing requirements in terms of properties that have to be fulfilled in order to be eligible for this designation. A document will only receive the Crystal Mark, when it can be **read**, **understood** and **acted upon** by the intended audience.[47]

The Plain English Campaign offers their service (for a fee) to revise and discuss any document until it fulfils the requirements for the Crystal Mark.

[41] Basara LR, Juergens JP. American Pharmacy NS34, 8:48-53. Patient package insert readability and design; 1994
[42] Baker SJ. Aust J Hos Pharm 27:126-131. Who can read Consumer information?; 1997
[43] Singh J. Dissertation. Richmond, VA; Virginia Commonwealth University. RAIN (Readability Assessment Instrument Manual). Development of an Alternative Methodology for Determining the Readability of Text; 1994
[44] The term 'validated / validation' is often used in this context. However, it is misleading as it is different to the term 'validation' in context with Module 3 of a dossier. Therefore the term 'verified / verification' is added to make the reader aware of this inconsistency.
[45] Doak CC, Doak LG, Root JH. Teaching patients with low literacy skills. 2nd edition Philadelphia: JB Lippincott; 1996
[46] Krass I, Svarstad BL, Bultmann D. Pat Edu Couns 47:29-36. Using alternative methodologies for evaluating patient medication leaflets; 2002
[47] http://www.plainenglish.co.uk/ (accessed 15.12.2006)

In the UK several PILs were redesigned and re-written by this process. They now bear the Crystal Mark. However, several crucial points obviously lack in this procedure, as the 'crystallising' process never is mentioned by CAs as a possibility for PL-testing. It is only mentioned in the MHRA guidance '*Always read the leaflet'* as a way to achieve a good quality of English.[48]

It remains to be seen from either further guidance or first experiences from industry if there might be a way to establish the Crystal Mark process as an alternative to Diagnostic Leaflet Testing, e.g. after developing a 'verification' data package.

⇒ In conclusion, **design assessment tools** should **not be ruled out** as an opportunity for PL-testing. However, it must be pointed out that appropriate validation/verification data are necessary and that it might be extremely time consuming and laborious to create them from scratch. Particular caution is advised when design assessment tools claim to be 'validated'. In most cases these 'validations' and their underlying data packages can not be regarded by the European CAs as an appropriate 'verification' that the design assessment tool is comparable to the gold standard of Diagnostic Leaflet Testing (section 2.1.4.1).

2.1.4 Direct patient-PL interaction tests

This group of tests concentrates on the PL itself as the object being tested. Interactions between the patient or the test person and the PL are seen as a process to elucidate how the PL can be improved or changed. It is not the human being that is being tested as described in the health literacy tests above.

2.1.4.1 Diagnostic Leaflet Testing - the method

The most prominent representative of this group of tests is the **Diagnostic Leaflet Testing**, which is based on the work of Sless. [15,22] It is also called the 'Australian testing method', and it has already been described by the EFPIA[16] and in EU-guidelines[11,13] and can be used and submitted to the CAs without the necessity for the applicant to be responsible for the respective validation/verification[44] data package. The major consecutive steps for this test method are:

- Designing and writing a PL according to Usability Guidelines[15]
- Compiling a tailor-made questionnaire for the PL
- Conducting diagnostic testing (interview) with a first round of ten participants
- Evaluation of results (comparison with acceptance criteria, section 2.2.2) and adaptation of PL, if necessary
- Repetition of diagnostic testing (interview) with a another round of ten participants
- Evaluation …

The cycle of interviews, evaluation and adaptation of PL is iteratively repeated until the acceptance criteria (section 2.2.2) are fulfilled for the last 20 tested persons.

This method is widely used and therefore the focus of this thesis. The next section (2.2 *Diagnostic (Leaflet) Testing*) exclusively concentrates on this method. Further details are given in Appendix 2.

[48] MHRA. Committee on Safety of Medicines: 'Always read the leaflet' Report of the Committee on Safety of Medicines Working Group on patient information. 2005 (available from the MHRA webpage)

2.1.4.2 PAINT-Consult written readability test

A further test method of this type (see also Appendix 2) was developed by Fuchs and is called the PAckage INsert test (PAINT).[49,50] This method is based on the Diagnostic Leaflet Testing described above. There are two major differences: The first is that the answers to the questionnaire about comprehensibility of the information provided by the PL are not given in an interview situation, but as a self-administered questionnaire by the patient. The second is that the questionnaire is a standard questionnaire, which is not tailored to the PL of the specific medicinal product. The author claims to have had the test as a whole validated.[49] In addition, he states that the PAINT-Consult written readability test received recognition in the MRP in March 2006.[51]

PAINT is acknowledged by the BfArM,[52] (German CA) which also points out the advantages of this test: There is no interviewer, who could possibly bias given answers and evaluations. However, this method is not 'free for use', as the accompanying data package for validation/verification is proprietary to PAINT-Consult.

2.1.4.3 CIRF (Consumer Information Rating Form)

With this self-administered questionnaire the authors claim to measure the comprehensibility, the utility, and the overall design quality of a PL. However, the question on comprehensibility is asked directly (i.e. 'How easy or hard is the leaflet to understand?'), instead of being evaluated indirectly. Therefore this method will certainly not be able to fulfil the expectations of assessors from European CAs.

2.1.4.4 P.A.P.I. (Psychological Analysis of Patient Information)

In contrast to the Diagnostic Leaflet Testing method mentioned above the P.A.P.I. method is not widely known. This approach was developed by 'Psychotechnisches Institut' in Austria.[53] It is quite different from using solely an oral or written questionnaire on facts about a PL as the central test part. The institute that has a marketing and a psychological background suggests a test method that claims to investigate

- the legibility and comprehensibility of the PL and
- the patient's emotions that are triggered by the PL itself and its wording.

The test is performed by a 'Creative Group' that '*studies subliminal views and ideas – the emotional, subconscious aspects of a topic – which the participants themselves are not consciously aware of.*'[53] This is achieved by a set of methods such as (see also Appendix 2):

- (structured) group discussions,
- drawings
- priority shots
- emotional distance scaling
- role playing
- benchmark test

[49] Fuchs J. BfArM im Dialog, 15 Februar 2006, Bonn. Entwicklung und Testung eines Instrumentes zur Beurteilung und Optimierung der Packungsbeilagen; 2006

[50] Fuchs J. Dissertation, Humboldt Universität Berlin. Die Packungsbeilagen als ein Mittel zur gezielten Information und Handlungsanleitung für Patienten. Entwicklung und Testung eines Instrumentes zur Beurteilung und Optimierung der Packungsbeilagen von Arzneimitteln; 2005

[51] http://www.paint-consult.com/uk/aktuell/index.htm (accessed 31.12. 2006)

[52] http://www.bfarm.de/cln_043/nn_424304/SharedDocs/FAQ/DE/Arzneimittel/pal/fa-ampal-faq.html (accessed 19. 2. 2007)

[53] http://www.psychotech.at/14_papihead.htm (accessed 1.2.2007)

The results of testing are measured in terms of legibility, comprehensibility, content analysis, emotionality, triggering of fears or non-compliance, perception of single statements, image transfer from PL to medicinal product, as well as from PL to MAH, and perception of the medicinal product (positioning).

It is important to point out that one part of the P.A.P.I. method is almost identical to the PAINT method. In one part of the structured 'Creative Group' discussion each participant is asked to fill in a questionnaire on the PL. This has to be done separately without any influence by other participants or an interviewer. The differences versus the PAINT are that

- no standard-questionnaire is used but a specific product-tailored one
- no repetitive testing is foreseen

In case the 90 % / 90 % benchmark (for benchmarks please refer to section 2.2.2 *Pass marks of Diagnostic (Leaflet) Testing* further below) is not reached, recommendations for improving the PL are made, aiming at the specific issues that failed. These recommendations also take into account all the other test results that emerged during the entire 'Creative Group' session.

⇒ In conclusion, **direct patient-PL interaction tests** generally **fulfil** the legal requirements of *consultations with target patient groups.* The Diagnostic Leaflet Testing is a 'ready to use' technique, whereas different approaches, which are similar but not identical, such as PAINT or P.A.P.I., have to be 'validated' or (better) 'verified' with a data package that shows their comparability to the Diagnostic Leaflet Testing as the gold standard at European CAs.

2.1.5 Acceptance for test methods

Although a wide range of described testing methods (section 2.1.1 – 2.1.4) exists, this number substantially shrinks when it comes to pick out the methods that will be accepted by CAs. The final estimation of applicability of the four major testing groups in order to fulfil legal requirements originating from *Directive 2001/83/EC as amended* Art 61(1) 2nd sentence and Art 59 (3) leads to the insight that the requested *consultations with target patient groups* are only achieved with a direct patient-PL interaction test (Tab.4).

The Readability Formulae and the Health literacy test do not feature the PL-specific consultation with a target patient group. Their results do not allow deducting whether the patient would be able to '*appropriately act upon the* (specific) *PL*'.

The design assessment tool does not directly implicate the *consultations with target patient groups* either, but there is a theoretical approach to '*bridge'* this missing aspect by providing 'validation' or 'verification'[44] data. However, at the time of this thesis, no widely known design assessment tool was established which is based on a 'verification' data package accepted by European CAs.

Besides the publicly described test methods, there naturally exists the opportunity to take the request for *consultations with target patient groups* quite verbatim. This would result in approaching patient organisations for specific diseases (*target patient groups*) [54, 55, 56, 57] and

[54] http://www.eurordis.org/sommaire.html (accessed 11.2.2007)
[55] http://www.ipopi.org/ (accessed 11.2.2007)
[56] http://www.patientsorganizations.org/ (accessed 11.2.2007)
[57] http://www.tsh.org/resources/patient.html (accessed 11.2.2007)

ask them to act as a *consultant* for the PL. This approach would probably not fail due to limited interest at patient organisations on the contrary, these organisations are very eager to get involved in the discussion on 'their medicines'. However, a missing structured process for the performance of these 'consultations' is currently seen as the major hindrance for this approach. The major obstacle is the difficulty in finding a way for an appropriate presentation towards the CAs. It is not sufficient to provide detailed protocols of the discussions, as CAs expect to receive a traceable description on why the patient will be able to act appropriately upon the PL.

It remains to be seen how the involvement of patient organisations will develop in the regulatory field. At the patient organisations it certainly would improve the understanding for the regulatory musts and limitations of MAHs and it probably would improve the PLs by setting a (more) target specific focus.

In Tab. 4 an overview of the test methods described in section 2.1.1 – 2.1.4 is given according to their main features and the resulting acceptance at CAs. The 'Consultation with patient organisations' is not included in this table, as there is too little experience with or literature on that approach.

Tab. 4: Summary of different characteristics for the four major 'Readability' testing groups and resulting acceptance by CAs with regards to *Directive 2001/83/EC as amended Art 59 (3) and 61 (1)*.

	Readability Formulae (Section 2.1.1)	**Health literacy tests** (Section 2.1.2)	**Design assessment tools** (Section 2.1.3)	**Direct patient-PL interaction test** (Section 2.1.4)
Object tested	Package leaflet (prose passages)	Person, who claims to be able to read	Package leaflet	Package leaflet
Person involved in actual test	None (only software)	Patient	None (only evaluator)	Patient
Subject Matter tested	Relationship between words per sentences and length of words.	Health literacy	Format and style supporting comprehensibility	'Usability' / ability to 'act upon'
Acceptance by CAs	None	None	Theoretically, if validated/verified with parallel interview-based data	Yes, if either performed according to the 'Diagnostic Leaflet Testing method' or based on a validated/verified method

When a pharmaceutical company has to decide which method of PL-testing to choose, there remain only a few alternatives, which are 'ready- to-use' in terms of acceptability by CAs and accessibility through CROs which are in the business of performance testing. The most prominent is the method of 'Diagnostic Leaflet Testing' originating from Australia.

In the following section the applicability of the Australian Diagnostic Leaflet Testing in the European context is discussed.

2.2 Diagnostic (Leaflet) Testing[58] – An Australian method in the European context

2.2.1 Implementation

Diagnostic testing was developed by Sless in the early 90ths. Its purpose was to answer the question: '*Can people use my information artefact in the way I have designed it to be used?*' A prerequisite for the testing process is the assumption that the problem lies in the design, not in the user.[59]

> '*The problems that users have are **symptoms** that there is something wrong with the artefact's design; **the method is called diagnostic testing** because it takes the symptoms seriously and uses them to diagnose and treat the pathological condition of the design.'*

EU guidelines[11] explicitly state that Diagnostic Leaflet Testing based on the Australian usability testing is only **one** method of complying with legal requirements. They also state that others methods will be accepted in case of appropriate documentation / validation. However, for most companies the method of Diagnostic Leaflet Testing is the preferred one, as it is well known that this method has generally a high acceptance at CAs.

What matters most in the regulator's world is the time factor. Therefore, companies, after weighing benefits against risks at the time when NML came into effect, chose to stick to the relatively well-known Diagnostic Leaflet Test. In consequence they neglected to take the risk to establish a different method, which they would first have to develop and then to verify ('validate').[44] Both would take so much time and resources that it was not deemed justified, considering the 'alternative approach' of taking a 'ready made' method, well-known to the CAs.

However, even the Diagnostic Leaflet Testing method has its drawbacks. Interestingly, they are mainly due to the way in which this Australian method was selectively implemented in the EU guidance documents rather than due to the method itself.

Sless himself commented on this topic as follows:[12]

> *'When the EU introduced its guideline on medicine labeling-patient information leaflets (PIL) in 1998 it copied many aspects of WMP: the performance benchmarks, the testing methods, and some of the advice on language use. **But it failed to copy the full range of structured writing and layout guidelines that were developed as a result of the iterative testing and refinement of medicines information that had preceded WMP.'***

Sless is very concerned about the 'Model leaflet' of Annex 1a of the Readability Guideline of 1998, because it violates '*… many basic principles of good information design'*. He also demonstrated some data derived from tests conducted by CRI(A) in Europe for a European Pharmaceutical company.[12] Although the product was quite simple and all information fitted on two sides of an A5 sheet of paper, the test failed due to the use of the structure of the model leaflet. Only three out of 13 participants reached the benchmark level of 81 %. Sless assigned the failure to the structure of the model leaflet. This problem persists, as the QRD templates, which replaced the 'model leaflet' do not differ substantially in their structure and strict order, in consequence regulators will keep putting square pegs into round holes.

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[58] Diagnostic Testing from AU is called Diagnostic Leaflet Testing throughout this thesis. See also section 1.2 on Terminology.

[59] Shrensky R, Sless D. CRIA publication. Choosing the right method for testing; 2005

It should be noted that not even Australia has a legal requirement to submit to its TGA results from Diagnostic Leaflet Testing or from any other test method. Therefore, no broad experience from dealing with Diagnostic Leaflet Testing in every day's life of CAs and MAHs could be gained up to now.

2.2.2 Pass marks of Diagnostic (Leaflet) Testing

Besides the general aspect of how the Australian method was implemented in European guidelines, it is particularly interesting to note how the pass marks or success criteria for this method vary, depending on the context in which the test method is mentioned (Fig. 3).

Readability Guideline 1998

Annex 2 of the 'old' Readability Guideline of 1998 states that the objective of the readability test is:

> *'To have at least **16 out of 20 consumers able to answer each question correctly.** However, it is not necessary for the same 16 people to answer each question correctly. It may be necessary to retest several times in order to achieve this level of performance.'*[13]

This amounts to a simple **80 % pass mark per question**. In the context of this Guideline to answer a question means to locate the information, rephrase it, and explain its meaning. Overall, this pass mark would allow for a maximum of 20 % 'people drop-out'.[60]

According to Sless[61] this European benchmark stems from the Australian WMP of 1994.[22] However, the key benchmark of that Usability guideline (WMP) is that '*100 % of literate people tested should be able to find and use at least 80 % of the information they look for'.* This means that there is no allowance for people drop-out. On the other hand there is allowance for up to 20 % 'question drop-out'.[62] The 'slightly' different wording used in Annex 2 of the 'old' Readability Guideline of 1998 leads to a completely different standard for pass marks (Fig. 3).

Draft Readability Guideline 2006

The Annex of the new Draft Readability Guideline of 2006 states the following:

> *'A satisfactory test outcome for the method outlined above is when 90 % of literate adults are able to find the information requested within the Package Leaflet, of whom 90 % can show that they understand it'.*[11]

It is not clear what the term 'information' stands for. Is it the whole set of information they are asked for, or is it meant to indicate the single questions? Anyhow this pass mark is a **person based double pass mark of 90 % of interviewees able to locate and 90 % of the latter able to understand**. This results in an overall minimum of 81 % of people who must be able to locate and understand 100 % of the information. There is no allowance for a 'question drop-out'.

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[60] 'People drop-out' means the theoretical situation that an interviewee is not able to answer a single question.
[61] Sless D. CRIA. Usable medicines information, Generalised principles and processes for designing usable labels and leaflets for medicine: a review of research and practice 1994-2001; 2001
[62] 'Question drop-out' means the theoretical situation that a question is not answered by a single interviewee.

As the Annex of the Draft Readability Guideline of 2006 is roughly a direct copy of the Annex of the UK-MHRA Guideline of 2005,[14] further explanation may be extrapolated from a Q&A paper[63] on the MHRA Guideline. This paper explicitly states:

> *'Each question must perform satisfactorily. …' (Answer no. 4) and*
> *'In general we would expect as a minimum for 18 out of 20 participants to find the information in the PIL and for a minimum of 16 out of 20 to be able to show that they can achieve the success criteria and it is not appropriate to sum the data.'*
> *(Answer no. 5)*

A comparison of the wording of the pass marks in the Draft Readability Guideline of 2006 and in the MHRA Guideline shows that they are almost identical to the pass mark in the Australian WMP of 1997 (Fig. 3). However, Sless summarised in 2001 his own WMP 90 % / 90 % pass marks of 1997 as follows:

> *'The benchmark requirement set by WMP was that **any person** who regards themselves as literate should be able to find 90 % of what they looked for on medicine labelling, and be able to use 90 % of what they found; 90 % of 90 % = 81 % success by any literate user.'* [61]

This interpretation is very much in line with his initial description of pass marks in the Australian WMP of 1994 (apart from the figures). It has to be clearly noted, that even though the Europeans meant to **copy** the Australian Usability testing together with all its success criteria, the outcome on European level as well as on national (UK) level has experienced a crucial **turn** in its requirements. They turned from the primary (Australian) intention that

- **any (literate) person can answer 80 % of the questions**

to the situation that

- **any question is answered by 80 % of the interviewees**

EFPIA 2003

In contrast to the straight positions about pass marks above, the EFPIA General Recommendations[64] present a more relaxed attitude: After referring to *' … at least 16 out of 20 consumers answering each question correctly (i.e. 80 %)'* from the Readability Guideline of 1998, the EFPIA states:

> *' … However since the overall assessment of the quality of the PL is more important than the achievement of any particular score, deviations on particular questions could be justified and acceptable. **Failure to individual questions should therefore not necessarily be considered as failure of the overall test.***
> *As per industry experience 80 % overall correct responses (**cumulative** across all subjects in a round of testing) shows an acceptable level of readability of the PL. For example, if the questionnaire has 10 questions and a total of 20 subjects are being tested, 160 correct answers out of 200 are needed to achieve the goal. This does not mean that every subject has to answer 80 % of the total questions correctly.'*

[63] MHRA. Additional Qs and As in relation to the new legal requirement to undertake consultation with target patient groups (Compliance with Art 59 (3) of Council directive 2001/83/EC); 29 June 2006

[64] EFPIA. General Recommendations for Readability user testing of Package leaflets for Medicinal products for Human Use Submitted or approved under the European Centralised procedure; March 2003

In summary, the EFPIA sticks to an overall 80 % pass mark. However, it is left open whether this is related to consumers (allowing up to 20 % of consumers to fail) or if it is related to the questions (allowing up to 20 % of the questions to fail). Considering the present situation, particularly the specific guidelines drawn up by CAs, one might certainly not consider these 'stretchable' EFPIA recommendations as any more applicable.

Sless 1994 - 2005

All pass marks are described above are either directly or indirectly derived from the Diagnostic (Leaflet) Testing approach in Australia, which is particularly the work done and published by Sless. Some interesting observations about benchmark minimum acceptable performance standards can be gathered from a recent (2005) publication:[65]

> *'… This* (the need for benchmarking) *is the origin of the 80 % benchmark performance standards for prescription medicines applied in 'Writing about Medicines for People (1994). In the more recent 'Labelling code of Practice (2004)' for non-prescription medicines, the benchmark is that* ***every person*** *tested should be able to find 90 % of the information on the label, and appropriately use the information 90 % of the time.'*

Apparently Sless draws a distinctive line between prescription and non-prescription medicines. Also the development of two different pass marks (one being 80°% the other 90 % / 90 %) is rather remarkable; especially as the 2nd edition of the *'Writing about Medicines for People (1997)'* by Sless also calls for the 90 % / 90 % person based pass mark. Obviously Sless now thinks in terms of further differentiation of the pass marks.

The comparison of various citations over several years is tedious work, therefore in the following Sless' citations are shown in utmost brevity:

- **1994**:[22] ***100 %*** *of literate people find and use at least 80 % of the information* (Prescription medicines)
- **1997**:[15] over 90 % of interviewees should be able to locate and 90 % of the latter able to understand the information
- **2001**:[61] *90 % of 90 % = 81 % success by* ***any*** *literate user*
- **2004**[66] / **2005**:[65] ***every person*** *tested should be able to find 90 % of the information on the label, and appropriately use the information 90 % of the time* (non-prescription medicine)

To make a long story short: Sless' intention was to ensure that **all** people could use the **most** of the information (i.e. '100 % of people', 'any user', or 'every person'). Only in one publication, the 1997 WMP guide, he did not use a clear-cut wording, but corrected himself in a later publication of 2001. Unfortunately, the Europeans chose a different wording when implementing the WMP of 1994 into the Readability guideline of 1998. In addition the UK chose for its national guidance the WMP of 1997 with the non clear-cut wording without investigating its context or actual intention. This resulted in different pass marks in European Guidelines and it remains to be seen if the opportunity is taken to adjust this in the final Readability Guideline of 200X.

[65] Sless D, Shrensky R. CRIA publication. Designing medicine information for people: an introduction to the course; 2005

[66] CRIA. CRIA Publication; medicine labelling code of practice; 2004

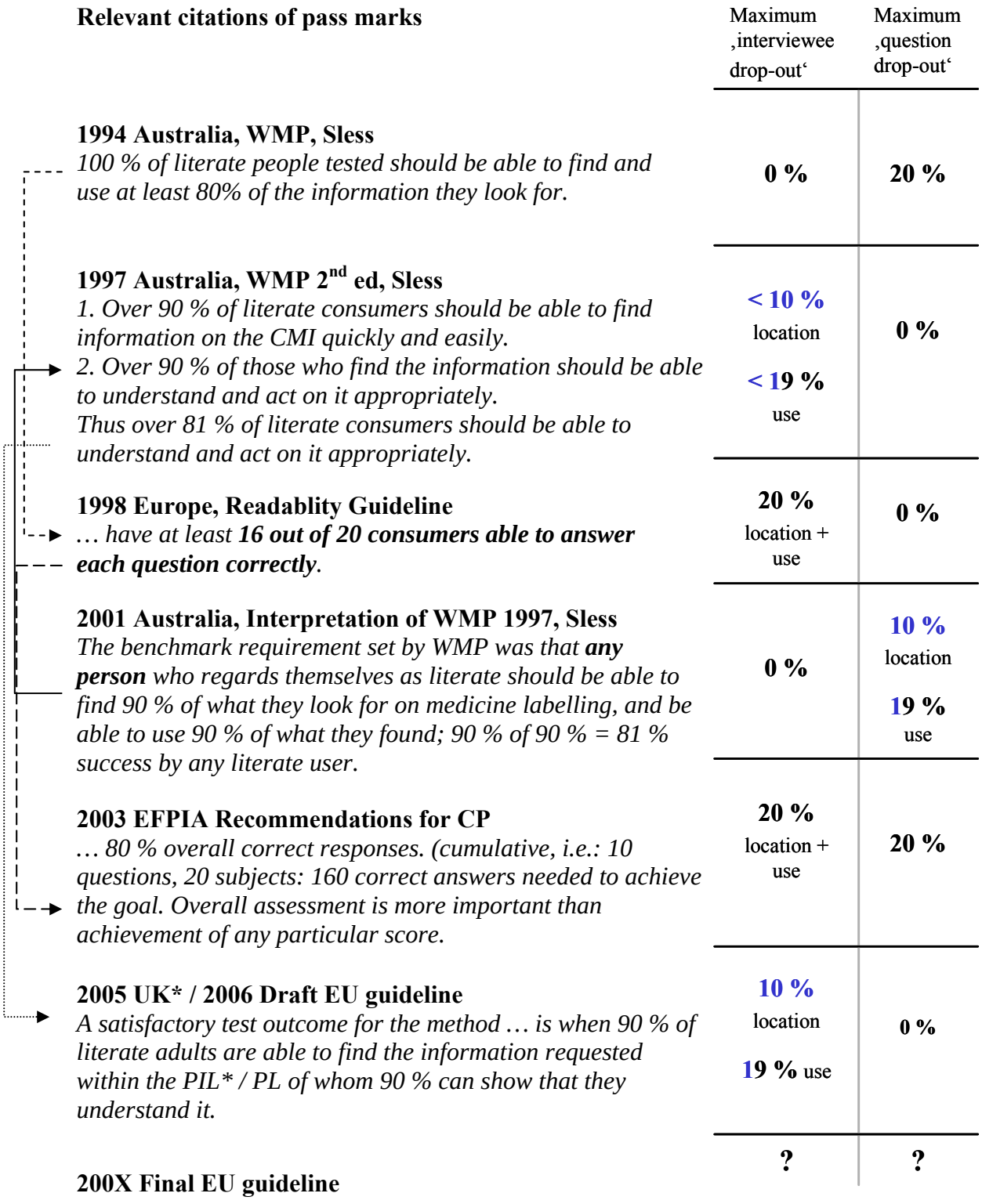

Fig. 3: Comparison of various citations for success criteria in Diagnostic Leaflet Testing. The text indicates the source and cites the respective definition. The arrows indicate which text was intended to be transferred to which document. The left column of the table describes the maximum of people that are allowed to fail completely. Blue colour indicates that for the split criteria amongst the 19 % use-fails must be the same 10 % that failed in locating the answer. The right column of the table shows the maximum percentage of questions that may fail.

2.3 Cooperation with a CRO for Diagnostic Leaflet Testing

A pharmaceutical company's decision to outsource Diagnostic Leaflet Testing mainly relates to the interview process itself and the evaluation of results. The process of writing an initial version of a harmonised PL stays with the medical experts of the pharmaceutical company. The underlying reason is that it is the MAH who is ultimately liable for the product and its accompanying information texts. Therefore the MAH has to decide on their content. Furthermore, after the experience of creating the SPC, it would not be too difficult for the company's experts to generate the corresponding PLs, if patient specific and regulatory requirements are taken into account. However, organising the actual process of Diagnostic Leaflet Testing with recruiting target patients and performing interviews is something that companies might be reluctant to implement on their own.

In the decision making process for selecting a CRO which can take over those tasks, it might be worthwhile to consider the varied histories of those organisations. There are four main backgrounds from which Diagnostic Leaflet Testing CROs originate and with each there are specific advantages and disadvantages for the client:

- **'Classical' Clinical Research Organisations**: These CROs are experienced in conducting clinical studies (Phase I-IV) with volunteers and patients. They are experienced in recruiting people and organising studies as well as writing documents which would be submitted to CAs. They are not necessarily expert in linguistic or translation aspects.
- **Translation agencies**. These agencies offer faithful translations of the final English PL version which have to be transmitted to the respective European CAs after a successful Diagnostic Leaflet Test and end of regulatory MR-procedure. There are quite a number of translation agencies which try to make their 'share' of the new requirements, by offering a 'full package' which consists of the Diagnostic Leaflet Test and the '*faithful'* translations in the required languages. Such agencies are not necessarily expert in organising studies, recruiting test persons or writing reports that meet the regulatory requirements.
- **University research departments** (on patient information): These departments are usually experienced in research on linguistic aspects as well as the patient's needs for information about a medicinal product for a long time. They have an in-depth knowledge of linguistic aspects and are experienced in interviewing people. They are not necessarily expert on processes within tight timelines or translations into other European languages. The lack of a basic medical knowledge also in some cases might hinder the overall process.
- **Marketing research companies**: Many pharmaceutical companies have a business relationship with marketing research companies as they often outsource the investigation of the marketing success of brochures, folding box design, and promotional material. A logical effect of NML was to approach marketing research companies and to ask whether they could add a test for the PL. A disadvantage of these marketing research companies might be that they are often not too familiar with regulatory requirements (besides advertising laws) or that their medicinal knowledge is too superficial. On the positive side these companies should be highly experienced in interviewing people and their employees probably have excellent writing skills.

A quite reasonable approach for the selection process of a CRO begins with inviting several firms to make presentations characterising their general capabilities and to discuss their testing approach in detail. If several PLs have to be tested, it might be advisable to start with two or three CROs in parallel. This helps the client compare the companies and chose the one that best meets his needs.

Three aspects have to be taken into account:

- There is no professional certification designation for PL testing companies. Therefore, the delivered quality has to be judged separately in every single case.
- There is a big backlog of PLs that need to be tested. This is due to the retroactive application of the NML. Therefore, some CROs may be oversubscribed, develop bottlenecks and may not be able to deliver as promptly as the client wishes. This may lead to the situation where the 'second choice' CRO has to be awarded the contract. Under these circumstances HQ may have to spend more time and effort to attain the level of quality needed.
- Diagnostic Leaflet Testing is not 'just another study' which is outsourced and only looked after when the results come back. It is a highly interactive process between CROs and MAHs.

The Draft Readability Guideline of 2006 states in Annex 1: '*Ideally the writer of the Package leaflet will carry out the interview, or occasionally accompany the interviewer during testing, to enable direct transfer of learning'.* However, in many cases this is not a realistic approach and the direct involvement in interviews has to be replaced by a lively interaction when preliminary results are provided. All proposals for re-wording, re-designing, or re-arranging the PL as well as the handling of the respective feedbacks must be discussed thoroughly.

2.4 Budget / resources

The total costs for PL harmonisation and Diagnostic Leaflet Testing are naturally dependent on the number of countries involved. In general there are always four relevant components:

- Employee man-hours of the pharmaceutical company (HQ and affiliates)
- CRO costs
- Translations costs
- Fees charged by the CAs for the regulatory procedure

The pharmaceutical company (HQ and affiliates) is faced with an additional workload as mentioned in the introduction of section 2 *Implementing a new process into established structures of a company.* A rough estimate of average time invested at a pharmaceutical company for PL harmonisation and subsequent Diagnostic Leaflet Testing was drawn from experience[67] with several MRPs involving up to 16 countries at a time:

- 10-30 h for project scoping and contract negotiation with PL-testing CRO
- 20-40 h for writing the first draft PL at HQ
- 3 x 2-3 h for checking the first draft PL by company-experts (pharmacovigilance, clinical, commercial)
- 2-3 h per country involved (3-16 countries) for checking the first draft PL by affiliates
- 30-40 h for review and discussion with CRO during several steps of PL-testing
- 3-5 h for creation of mock-ups for several steps of PL-testing
- 20-30 h for compilation and submission of dossier to affiliates
- 3-4 h per country involved (3-16 countries) for checking the translations for final PL
- 10-50 h for discussion and filing of 'Answers to Objections'
- 10-20 h per country involved (3-16 countries) for overall interaction with their CAs (compiling and filing of initial dossier, answers to objections)

At HQ this would add up to approximately 100-200 h of time spent per single PL that is harmonised and tested. This equals approximately 2.5-5 weeks of pure working time in total.

[67] personal experience of the author of this thesis

This total does not include any training time needed to bring the people involved up to speed. For each affiliate involved the time would add up to 15-27 h for each PL that is harmonised and tested.

As an example, a PL of a MRP for 14 countries involved would require a total time commitment of 310 - 578 h (equivalent to approximately 8-15 weeks) across the entire company.

In order to get a rough idea about the costs behind these numbers a rough estimation was done on the basis of an average salary in Germany in the area of chemistry / pharmaceutical,[68] which on average for both genders is 42,463 € per year. For the company this adds up (doubles) to 84,926 € per man-year including taxes and tributes. Despite the immense uncertainties when time is transferred to money the 8-15 European working weeks mentioned above would be **13,000 – 25,000 € per leaflet** as total **internal costs** for the company (with an average of 19,000 €).

In addition, the costs for the **CRO** have to be considered. They are **12,000 – 35,000 €** per PL to be tested, with an average of about 15,000 €. It has to be mentioned that costs certainly depend on the different CROs and the number of PLs tested (e.g. 'test 9 PLs, get one free').

Translations add considerably to the overall costs, depending on the length of the text as well as the specific language needed.

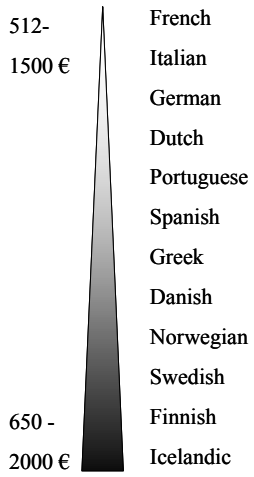

Fig. 4: Costs for translations from English into an exemplary set of languages on the basis of a 2,000 word PL. Numbers do **not** take into account the check of source documents (SPC), the translation instructions, the peer-review checks, the adaptation to QRD templates, the CRO project management, and the generation of files for additional names or strengths. This 'all-inclusive' service would raise the costs 4-5 fold.

An 'all-inclusive' translation service for a PL (Fig. 4) into 12 different languages with three strengths in total costs **75,000 – 125,000 €** (with an average of 100,000 €). The basic translation as part of the total would be up to **18,000 – 24,000 €.**

Interestingly, some UK located CROs calculate their basic translation fees on the basis of a ~ 800 word leaflet, which has been chosen to represent the current standard volume of UK PLs. The average length of harmonised English PLs according to QRD templates amounts to 2,000 words.

Fees for authorities must be broken out when summarising the financial aspect of PL harmonisation, PL testing, and PL assessment. A 'voluntary' Type II Variation with about 14

[68] http://www.gehalts-check.de/Gehaltsfuehrer/Gehalt-Office/BRA/BRA_19/BRA_19.HTM (accessed 12 November 2006)

of the 'old' European countries would cost up to approximately **30,000 - 40,000 €** (average of 35,000 €). Apart from the 'phasing-in' aspect this cost might be one of the reasons why companies wait until they are urged to submit a variation due to other requirements, instead of using the 'proactive approach'.

In total, an average harmonised and tested MRP PL (14 countries) would cost up to **169**,**000 €**. This number is composed of the above mentioned average costs: 19,000 € (working time) + 15,000 € (CRO) + 100,000 € (translation) + 35,000 € (fees).

2.5 Company internal timelines for the PL harmonisation including PL-testing

The process of harmonising and testing a PL for an established MRP product is a highly complex matter due to the large number of involved parties, as well as demands associated with the regulatory life-cycle of the product in question. As will be further discussed in the next section (2.6 *Timing of PL harmonisation and PL-testing – integration in regulatory procedur*es) the PL harmonisation process and PL-testing of MRP products approved before October 2005 do not necessarily have to be performed at once. Whereas the necessity for PL-testing might not be given for all products, the harmonisation of PLs should be done as early as possible and at least concurrent with the next upcoming (major) regulatory action.[5]

Please refer to the next section (2.6) for a discussion of the optimal timing and fit of this process with the regulatory procedures at CAs.

Company-**internal** timelines must take into account several aspects:

- Who is involved?
  - People responsible for PL drafting
  - People responsible for PL review (different company units such as regulatory affairs, pharmacovigilance, commercial, medical, affiliates)
  - CRO performing the Diagnostic Leaflet Testing
  - People responsible for CRO contracting
- How much time is needed for each action?
- How much time is needed for communication between involved parties?
- How does the workflow look like? Are there repetitive steps?
- Is there any target-submission date or target-approval date that is obligatory to meet?

In general, the organisation of PL harmonisation and PL-testing follows the classic rules of project management. Therefore, the initial planning to establish timelines should follow a realistic approach that reflects available resources and 'working tasks' with average timelines. In addition, some 'time buffer' must be added for worst-case scenarios.

A practical approach is to assign fixed dates to the work before submission (Fig. 5) and to have 'moving target dates' for the time after submission, i.e. during the MR phase and the national phase (Tab. 5). This is when the MAH is no longer in control of the approval process timelines due to interaction with and demands of the CAs.

Overall, an average time of about four months should be allowed for when starting from a 'ready for submission' MRP-SPC towards a 'ready for submission' MRP-PL. The average testing process at the CRO takes about 8 - 10 weeks.

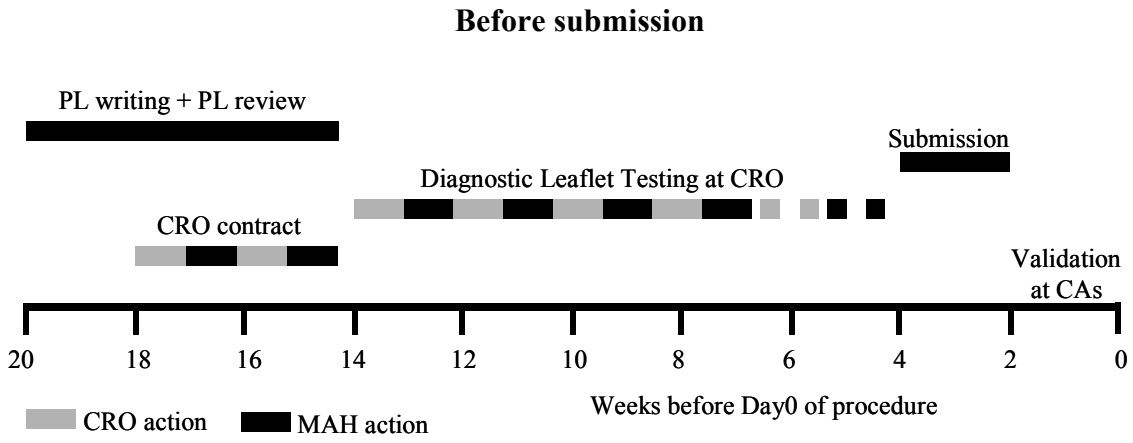

Fig. 5: Timelines for the PL harmonisation including Diagnostic Leaflet Testing before submission to CA. The example shows a situation where the creation and the testing of a MRP-PL is needed as a prerequisite for the submission of a type II variation for a new indication. Depending on upcoming issues concerning resources, availability of people, and shifting of focus the timelines must be adapted by project management. During the PL-testing process close interaction between the CRO and the MAH is essential to obtain optimal results.

During MR phase and national phase

In most MRPs two important stages require immediate action by the MAH. The first is the '*request for supplementary information'* (RSI) by the RMS, the second is the announcement of the '*end of procedure'* by the RMS (Tab. 5).

The content of the RSI can vary tremendously. The MAH gets a first idea about upcoming issues, when the Preliminary (Variation) Assessment Report (P(V)AR) is distributed to the CMS and the MAH several days before the official request is made. Normally, a whole range of requests or questions can be expected that aim at the scientific content of the PL as well as at design aspects (for examples see section 3.3 *Impact on PL during MRP phase*). The MAH has to ensure that people with the required expertise are available to submit the requested information in due time. In most cases this includes a new version of the PL with highlighted revised changes and also a clean version.

The second step calling for immediate action is the 'end of procedure'. Shortly afterwards the national phase of the variation or renewal has to be started by submitting the translations of the final agreed PL (and labelling). According to the Best Practice Guide (BPG) on variations[69] which has recently been updated, the MAH has to submit these translations within **10 working days** after the 'end of procedure' has been declared. The Final Assessment Report (FAR) allows to draw conclusions whether or not the proposal for the new PL was accepted (initial and/or revised version). Unfortunately, the last revision of the BPG on variations[69] in June 2006 missed the opportunity to amend the list of documents to be distributed by the RMS with an 'end of procedure' announcement to include the PL and labelling.[70] Therefore, the PL version submitted in response to the RSI has to be revised in case the final assessment report demands it.

MAHs must be well aware of the timeline statement made in the CMD(h) guidance document on the implementation of NML (Q 16).[5] '*High quality translation of the agreed SPC, PL, and*

[69] CMD(h) Best practice guides for the submission and processing of variations in the mutual recognition procedure Rev 4, June 2006

[70] CMD(h) Best Practice guide for the handling of variations in the mutual recognition procedure, Chapter 5: Type II variations (Revision 3, June 2006) mentions in section 14 only the SPC that has to be distributed by the RMS after the variation is approved.

*Labelling should be submitted **at the latest 5 days after the end of procedure**; however these may be required earlier in the procedure by some Competent Authorities*.' This statement refers to variations or renewals.

In either case, 10 working days[69] or 5 (calendar) days,[5] it is a rather short time frame. Therefore, the MAH must be well prepared by arranging the basic translations of latest submitted PL version including Blue Box Concept information for different countries. Besides that the MAH should set up a process that enables the submission of a PL version translated into one of the required languages on short notice.

Tab. 5: Moving target dates after submission (from the timetables of three types of MR procedures). Only the actions relevant for the MAH are shown. There are two major steps when the MAH has to react immediately on a well prepared basis: Firstly to answer to the RSI and secondly to submit the national version of the mutually agreed (final) texts after the end of procedure. As timetables for every separate procedure are constantly adjusted it is not possible to predict precisely at Day 0 when further actions will be necessary.

Renewal	Variation Type II (60 D)	Variation Type II (90 D)	RMS Action	MAH Action
Day 0	Day 0	Day 0		
Day 59	Day 59	Day 89	RSI to MAH	-
Day 59 + 30 (max) days	Day 59 + 60 (max) days + 60(max) days	Day 89 + 90 (max) days + 60 (max) days	-	Submission of requested information to RMS within given timeframe Start of basic translations of latest submitted PL version
Day 90	Day 90	Day 120	Announcement of 'end of procedure'; Circulation of final SPC, FAR	-
Day 90 + 5 (calendar) or 10 (working) days	Day 90 + 5 (calendar) or 10 (working) days	Day 120 + 5 (calendar) or 10 (working) days	-	Submission of national translation of SPC / PL / Labelling in accordance with FAR to CAs within 5 (calendar) or 10 (working) days
Day 90 + 5/10 days + 30 days	Day 90 + 5/10 days + 30 days	Day 120 + 5/10 days + 30 days	Approval of national texts	-

2.6 Timing of PL harmonisation and PL-testing – integration into regulatory procedures

Timing of PL harmonisation and PL-testing firstly needs to clarify the necessity for those processes. In order to throw some light on the complexity of procedures, conditions, and circumstances there are a few basic questions to be asked that might help to find the way through these steps:

- What type of application is intended?
- Is PL harmonisation mandatory / necessary?
- Is PL-testing mandatory / necessary?
- What supporting guidance is available?

In the following discussion some hints are identified on what answers might be given are identified. They are sorted according to the main types of regulatory procedures that exist in Europe. Recollection of the fact that PL harmonisation and PL-testing are not automatically linked to each other might also provide some insight to the process.

Later on this section dwells on the various regulatory actions that might be taken for an MRP product. Special focus is given on the question concerning whether these new requirements might delay planned regulatory actions compared to the situation before NML.

2.6.1 Centralised Procedure (CP)

New applications require a single, tested PL to obtain the MA by the CP. A proposal for that PL has to be submitted with the initial submission, whereas the results of PL-testing might be submitted as late as Day 121, if agreed upon with the EMEA and (Co-) Rapporteur in advance.[71]

In terms of established MAs (authorised before 20 November 2005) 'harmonised' PLs already exist, since single PLs have been mandatory with the introduction of CPs in 1995. However, in most cases there has been no PL-testing performed, as this was only recommended, but not mandatory.[72] In general, it is not mandatory to have the CP-PLs assessed retroactively. However, MAHs are advised to discuss this topic with the Rapporteur on the occasion of major variations, e.g. a new indication. Therefore, a factual possibility exists that the MAH will be obliged retroactively to perform PL-testing of 'established' CP products.

2.6.2 Decentralised Procedure (DCP)

New applications require a single, tested PL to obtain the MA by the DCP. A proposal for the harmonised PL has to be submitted with the initial submission, whereas results of PL-testing might be submitted as late as Day 106, if agreed upon with the RMS in advance.[73,75]

No established MAs exist as there are no MAs granted via the DCP before the NML came into force. The DCP itself was newly introduced by the NML.

2.6.3 National Procedures

New applications require the submission of a tested leaflet to obtain the MA via a national procedure. This might vary from country to country depending on how and when the NML was transposed into national law. As there should be no other European country with the same product already authorised, no 'harmonisation' is necessary.

In terms of established MAs, i.e. for national MAs authorised before the NML was transposed into national law, there is in general a deadline, by which the PLs available on the market should comply with the new requirements. However, the interpretation of how compliance has to be demonstrated varies from country to country. A quite strict interpretation is given by the MHRA guideline[74] that requires all PLs to be tested by 1 July 2008 at the latest.

These considerations lead to the MRP products, as there are always 'purely national' and 'national' MAs that have to be taken into account.

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[71] EMEA. Operational Procedure on Handling 'Consultation with target patient groups' on package leaflets (PL) for centrally authorised products for human use; 20 October 2005

[72] EMEA. QRD Group guidance on User testing of package leaflets for centrally authorised products for human use; December 1999

[73] CMD(h). Decentralised Procedure Member States' Standard Operating Procedure; October 2005

[74] MHRA. Guidance on the user testing of patient information leaflets; June 2005

2.6.4 Mutual Recognition Procedure (MRP)

New applications require the submission of a one single, tested PL to obtain a MA by the MRP. There is no question about harmonisation, since no divergent versions of the reference product (should) exist. However, if the PL of the reference medicinal product is not yet in line with the NML, the PL might have to be re-written. In any case PL-testing is mandatory. Further 'new applications' by second wave MRPs require a proposed harmonised and tested PL at the time of submission[5] from 1 November 2006 onwards.[75] During a transition period of one year (30 October 2005 - 1 November 2006) there existed the possibility of applying for a second wave MRP in parallel with a type II variation, the latter leading to a harmonised PL.

In terms of established MAs, i.e. for MRP-products authorised before October 2005, there is a constant reminder by the authorities that '*the new legislation is effective from the date of entry into force'*.[76] Therefore, the CMD(h) recommends '*to **harmonise** the labelling and the package leaflet of existing medicinal products **as early as possible** (at the occasion of a major variation or renewal procedure).'*

Until January 2007, there has been an astonishingly clear *'No … , nevertheless…*' answer to the question whether PL-testing will be required for medicinal products authorised before NML came into force. The conclusion from this answer[77] was that in general there is no requirement of PL-testing for those products. However, it leaves the loophole that the need for PL-testing has to be discussed with the RMS, since it has to be '*taken into account'* that '*consultation with target patient groups may be required at the time of variations introducing major changes to the package leaflet (e.g. use in a new target patient group, novel presentation with critical administration issues.)'* Observing the modus operandi of the French agency showed for example that this circumstance is interpreted as '*As soon as safety-information is changed, we strongly recommend PL-testing.'* and subsequently raises the question whether a PL can be harmonised without changing at least some safety information for any of the countries.

A consequence of this imprecise wording in the CMD(h) guidance document was its revision in January 2007. The answer[78] now solely states that '*Consideration should be given to undertaking consultation with target patient groups'* and the wording regarding the need for PL-testing changed from '***may be** required'* towards '***is** required'* in case of major variations.

In summary, the need to harmonise PL and labelling as soon as possible is a clear-cut fact for established MRP products. Concomitantly, the need to provide the results of PL-testing as well is regarded as necessary in most cases.

Special consideration, should be given to the various national requirements throughout Europe. The trigger for MAH's activities might depend on the **national transition periods** established by the EU countries for their national implementation of the EU law. Until when must the national PLs fulfil the overall European PL requirements? For example, in the UK the transition periods end by 1 July 2008. Therefore, if UK is included in the concerned countries of a MRP-product it would be wise to harmonise (and test) the MR PL instead of testing the current UK PL (without harmonising it for the EU). This could avoid spending twice the time and the money for PL-testing of one MRP product.

The impact that the new obligations (PL harmonisation and PL-testing) have on the timelines for regulatory actions for established MRP products is shown in Tab. 6. Focus was placed on

[75] Report from the CMD(h) meeting held 29th and 30th May 2006
[76] Question 22 in CMD(h) Q&As on the implementation of the new legislation. January 2007
[77] Question 18 CMD(h) Q&As on the implementation of the new legislation. October 2006
[78] Question 17 CMD(h) Q&As on the implementation of the new legislation. January 2007

the question whether the submission is delayed or changed (compared to the situation before the NML).

Tab. 6: Overview of regulatory procedures for MR products showing the implications for the need of PL harmonisation and PL-testing. The implication on timelines for submission to authorities is indicated in blue (compared to the situation before NML came into force).

Regulatory process	PL harmonisation	PL-testing
Renewal	Mandatory (retroactively) implications: Earlier onset of work (in addition to shorter deadline for submission)	Mandatory (retroactively) Timing of PL-testing is negotiable (before (a) or after (b) renewal); depends on RMS/CMS. Implications: a) Earlier onset of work (in addition to shorter deadline for submission) b) Type II variation after renewal
(Non-)Variation 61 (3)	Not applicable if not harmonised	Not mandatory - no delay
Variation IA	Not mandatory - no delay	Not mandatory - no delay
Variation IB	Not mandatory - no delay	Not mandatory - no delay
Variation II New indication	Mandatory at time of submission – **slight delay**	Mandatory at time of submission – **several weeks / months delay**
Variation II Safety concerned	Mandatory at time of submission – **slight delay**	Most probable mandatory – length of **delay** depends on RMS / CMS and the possibility to submit results during procedure instead of 'at time of submission'
New application (MRP)	Not applicable, as no divergent PLs exist	Mandatory (in most cases the reference product PL is not yet assessed for usability by patients)
Second wave MRP before 1.11.2006	Mandatory (via type II variation Until 1.11.2006 possibility for parallel procedures (with one common timetable)	Mandatory / waiver Depends on RMS / CMS
Second wave MRP after 1.11.2006	Mandatory at time of submission – **slight delay**	Mandatory at time of submission – **several weeks / months delay**

Particularly for the scenarios 'Variation II / New indication' and 'Second wave MRP' considerable delays in the date of submission have to be taken into account, because PL harmonisation and PL-testing have to be available at the time of initial submission.

In comparison to the CP and the DCP, where submission of PL-testing is possible as late as Day 121 or Day 106, respectively, it is not obvious, why the MAHs of MR products should be prevented from taking any initial comments of CMS and RMS into account before PL-testing is started. The DCP Standard Operating Procedure[73] makes obvious that similar considerations resulted in the possibility of the applicant to wait for initial comment from the RMS (i.e. until the draft assessment report). After learning about the RMS's position on the proposed management of user testing or its position towards a justification from the MAH concerning the omission of user testing the applicant can react appropriately. He also has the option to wait for the comments of the CMSs, before he modifies the PL prior to the start of a PL-test.

The Q&A document on the implementation of NML[5] theoretically also allows for MRPs the opportunity to '*consider the timing of consultation within the procedural timeframe*' (Question 20). However, this step must be agreed upon with the RMS beforehand. Current

practice comments from RMS are: *'…it would be ok for us if you do it along the procedure, but we are not sure, if the CMS would agree on that. There is potential that application will not be validated if test is not submitted before Day 0.'*

A reason for the exception with MRPs (in contrast to DCPs) might be that the theoretical consideration that a MRP regulatory action should be based on a product with an already harmonised (and possibly assessed) PL. However, as long as this situation is not the case for a considerable number of MRP products, and as most PLs have to go through a harmonisation process prior to other actions, it might be most sensible to allow the running of PL-testing in parallel to the regulatory action. The benefits would be:

- The submission (and time to market) would not be delayed due to the PL-testing process
- The tested PL could already reflect initial comments from CMS and RMS resulting in an accelerated dialogue and arrival at the 'final version'.

2.7 Technical and design considerations

In most European countries the layout of the PL has always been the responsibility of the MAHs. The result in a 'free market economy' system is that each MAH developed his own house style over time. Decisions on font size, font typeface and style, text orientation (landscape or portrait), booklet, A5, A4, as well as use of colours or columns have been up to the various MAHs. Although some recommendations existed in the Readability Guideline of 1998, the latitude for designing PL layouts was very wide.

Alongside the new requirements for PL harmonisation and PL-testing concomitant new guidance, such as QRD templates, Draft Readability Guideline, and Blue Box Concept obligations evolved. Therefore, some of the major layout parameters, such as colour, font size, paper format, or the use of pictograms have at least to be reconsidered by the MAHs.

Colour
Colour printing of PLs is more expensive than printing in black and white. Up to now it was at the discretion of the MAH what to prefer. However, with the NtA, Chapter 7, Section 10 in place, coloured PLs are now necessary at least for a few countries if their CAs insist on the listed 'Blue Box Concept' requirements:

- AT: The use of a pictogram (red triangle) for medicines which cause tiredness is obligatory.
- SE, SI, NO: The legal status and some information about indications and dosage must be stated in one or possibly several blue box(es) in the PL.

On the other hand, MAHs in NO and SE have been informed by their CAs that these blue boxes would not be required[19] (except for the actual text). Generally, there is no clear-cut answer to the question, if the use of colour would enhance the 'readability' of PLs and various opinions exist, ranging from 'being useful' to being 'too childish'. A survey by an Italian group demonstrated the reluctant position of patients towards the use of colour in PLs.[79] The outcome was that 65.7 % of the respondents did not like coloured PLs. The given explanation was '… *that people associate colour with other commercial products and think that a serious message, such as that reported in PL, loses scientific meaning and becomes an advertising message for a generic commercial product'.*

[79] Bernardini C, Ambrogi V, Fardella G. *et al* : How to improve the Readability of the patient package leaflet: A survey on the use of colour, print size and layout; 2001

Font size
This issue became quite conversant with the publication of the Draft Readability Guideline in September 2006[11], which states '*Where practical, your font size should generally be **12 point** for the main body of the text'.* This was perceived rather negatively by the pharmaceutical companies, as the last version of the Readability Guideline[13] stated '*The particulars appearing in the leaflet should be printed in characters of at least **8 point Didot**, …* '
Even when points (= 0.353 mm) are not as high as Didot points (= 0.376 mm), this is an increase of 41 % in the height of characters. This more than doubles the amount of space or paper needed, as characters and line spacing are a two dimensional issue.

Two well-known pro's and con's of **bigger font size** are:

- **Pro:** The legibility (in terms of decoding single words) is better.
- **Con:** The overall readability (in terms of comprehensibility) decreases as there are fewer characters per line, i.e. more lines per context issue. The 'physical act' to move the eyes from line to line distracts. The overall physical length of PLs increases leading to more 'square meters' of information. This is negatively perceived by patients.

Size of package leaflets
PL size is often determined by the machinery that assembles the carton, the primary packaging, and the PL. Standard machinery that moves the printed PLs via vacuum systems to the folding and assembling line delivers optimal results, when it copes with one-, two-, or three-folds of a standard size sheet (e.g. 297 mm x 175 mm). The use of non-standard sizes increases the percentage of the machinery's failures in the assembling process.

An average PL with approximately 2,000 words (English version) would fit nicely on a one-fold standard size sheet, if it is printed on both sides with 9 pt font size.

Assuming, this mock-up of the PL passes the PL-testing without considerable changes as to the amount of text or the size of fonts, the following questions have to be considered for the decision whether or not it will be feasible to keep the design with all national languages.

- The required space for translations will increase in length (Appendix1). Therefore, the major question is: Although the content stays the same how can one accommodate the increased need for area?
  Two options are imaginable:
  - Should the font size be decreased to 8 pt in order to keep the (tested) amount of paper, i.e. a one-fold standard size PL printed on both sides?
  - Should the (tested) font size be kept and the PL size be increased to 2-fold standard size with text covering the entire front page and continuing on the reverse side using approximately 10 % of it? This would leave approximately 90 % of the back-page blank.
- How does the Blue Box Concept information impact the space needed? In case the (tested) font size will be kept, in quite a few languages the size of a 1-fold standard size PL will not be sufficient and 2-fold standard-size has to be used bringing the same problems as stated above.

Pictograms, Symbols, Graphics, Images

Art 62 of *Directive 2001/83/EC as amended* states that '*The outer packaging and the package leaflet may include **symbols or pictograms** designed to clarify certain information …'.* The Readability Guideline of 1998 limits this in Section C – 3.3 to **pictograms** as an additional measure to make the message clearer to the patient.
However, the Draft Readability Guideline of September 2006 interprets Art 62 as permitting the '*use of **images, pictograms and other graphics** to aid the comprehension of the*

information …'. It further states that '***Symbols*** *and pictograms … should only be used to aid navigation, clarify or highlight certain aspects and should not replace the actual text.'*

A welcome application of pictograms with a positive impact of pictograms might be their use for easier navigation through the PL. In this respect pictograms could be used to amend the main headings or subheadings of particular importance such as for contraindications, interactions, use during pregnancy (etc.). However, currently no international (or at least European-wide) agreement exists at CAs on how the symbols or pictograms should look like (if used at all) for harmonised PLs, e.g. to aid navigating a PL. Therefore, its use is not a feasible approach at the moment. In addition, the Draft Readability Guideline of September 2006, foreseeing upcoming difficulties with the perception of pictograms throughout Europe, states that ' *Particular care will be needed when symbols are transferred or used in other language versions of the PL and further user testing of these may be necessary.'* This possible request will definitely lead to avoidance of symbols and pictograms used in the main body text/layout of a harmonised PL. As currently, the use of symbols and pictograms would then be restricted to the Blue Box Concept part of harmonised PLs.

Current examples for symbols required as Blue Box Concept elements, e.g. the warning about the effects of the medicine when driving or operating machinery, vary a lot between EU countries (Fig. 6). This indicates how difficult it might be to come to an agreement on EU level.

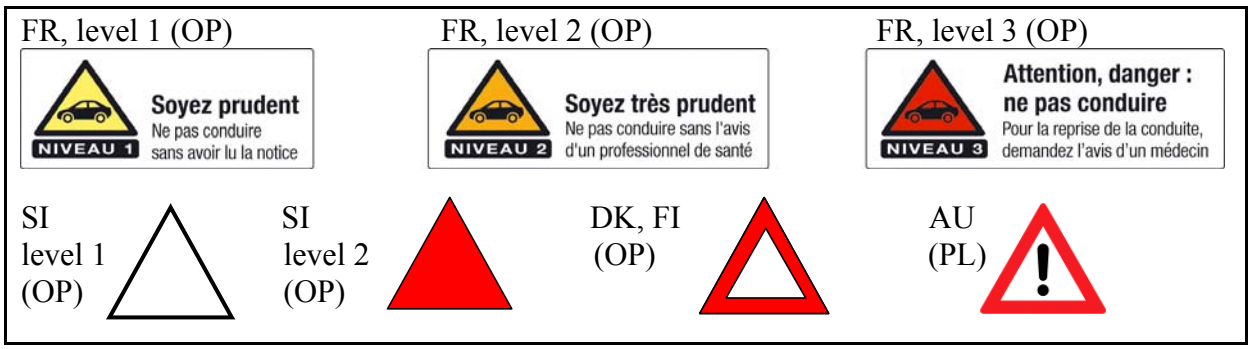


Fig. 6: Pictograms for warning triangles. All pictograms are mandatory as Blue Box Concept requirements for the respective countries to appear either on the outer packaging (OP) or on the PL of national or decentralised procedures (NtA, Chapter 7, section10). This example shows that it is obviously very difficult to come to a common position for all or at least several countries within Europe. In DK the same pictogram is used for three different warning levels, and the differentiation is made by the PL text that explaining the warning triangle.

The issue of pictograms in PLs was also investigated by a group in Italy.[80] They evaluated the preference of about 1,000 participants for various pictograms to have one preferred symbol for each heading within the PL (therapeutic indications, side effects, paediatric use, contraindications, use in pregnancy). For each heading a selection of five symbols was offered. The results showed no clear solution as answers varied strongly depending on age or educational background of the interviewed person. Just for 'paediatric use' and 'use in pregnancy' a slight absolute majority chose one of the five symbols.

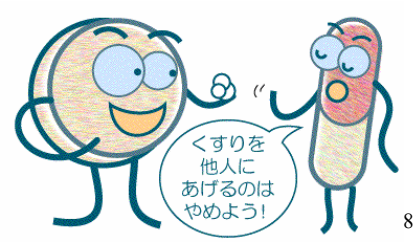
Paediatric use: 

Use in pregnancy: 

[80] Bernardini C, Ambrogi V, Peroli L, *et al*.. Pharmacol R 41:679-688. Comprehensibility of the package leaflets of all medicinal products for human use: as questionnaire survey about the use of symbols and pictograms; 2000

Overall, with no European wide accepted pictograms 'ready for use' in place, MAHs will stick to the mandatory pictograms instead of being creative. Besides the question whether a chosen pictogram is understood by the addressees also the 'style' plays a major role with respect to acceptance by the users as well as the technical applicability. For example the section 'Interactions' could be 'pictogrammed' in the following to ways:

[89] or



[81]

For a theoretical way forward to a set of accepted, 'ready for use' pictograms please refer to section 4.5 *Future for European PLs*.

Deviation from QRD templates?

Every MAH who tries to honestly apply the QRD template to his PLs will sooner or later ask to deviate a 'little bit' from this concise template. According to the annotated template this is allowed in a specified manner (such as to add sub-headings). However, nothing is said explicitly about the order of headings, the omission of subheadings, or a change of wording in main headings.
The major reproach made against the QRD templates is that it was not 'tested' for usability, that it does not reflect the patient's needs, and that it contradicts some of the recommendations of the Draft Readability Guideline[11] such as to avoid words in all caps or to use active wording ('Do not store above 25°C.'). Some CAs explicitly allow for deviation from the QRD templates (MHRA/UK)[82] or even ask for it at the national level (MEB/NL).[83]
The feedback from CROs during PL-testing sometimes relates to predefined parts of the templates. As an example the subheading 'Driving and using machi**nes**' is proposed to change into 'Driving and using machi**nery**'. The latter is considered as 'correct English'.

Although it might be tempting to deviate from QRD templates, MAHs should carefully weigh if short term gain may cause long term pain. This risk-assessment must be done particularly in the wake of future submissions based on the Product Information Management system (PIM) for decentralised and even national applications.

PIM is a major step towards purely electronically submitted application dossiers.[84] PIM applies to SPC, PL and labelling and is basically an xml based Data Exchange Standard (DES) developed on the QRD templates as 'backbone'.[85] Currently PIM can be used for pilot submissions in the CPs on voluntary basis, but in near future is will be also available for decentralised procedures[86] and even national procedures. Using the QRD templates as a backbone the QRD structures and headings serve as 'vertebral bodies'. If they are changed or omitted there is a high probability that the backbone collapses as soon as PIM is applied.

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[81] http://www.pmda.go.jp/kusuri/ku1.html; pictogram used for highlighting the danger of passing prescribed medicinal products on to others. (accessed 10.1.2007)
[82] ABPI User testing workshop; 20 September 2006
[83] MEB-5-3.0 EN: MEB Package leaflet of pharmaceutical products; 22. 1. 2004
[84] Menges K. Pharm Ind 68:400-408. Das Produktinformations-Management-System (PIM) im europäischen Netzwerk von Arzneimittelzulassungen; 2006
[85] http://pim.emea.europa.eu/whatispim.htm (accessed 27. 1. 2007)
[86] MRFG/CMD(h): Concept paper – achieving harmonised patient information; September 2005

3 PL content affecting milestones before and during MR Procedures

Before the legal requirement of PL-testing accompanied by the need for harmonised PLs in MRPs came into force, the content and design of national PLs was mainly influenced by CAs in the national phase. Every European country had its own method of how to fulfil the requirements to provide PLs according to *Directives 92/27/EEC* or *2001/83/EC* (not amended). At present there are various circumstances that might lead to substantial changes of the PLs in Europe. This as seen from a national point of view by comparison of 'old' PLs with 'current' PLs, that fulfil pertinent legal obligations.

On the way from national PLs of an 'established' MRP product (dated before October 2005) towards 'current' national PLs, these must be are harmonised, qualified by Diagnostic Leaflet Testing, and approved by national CAs. The four major steps affecting content and design of PLs during these procedures shall be described in the following sections:

- **Creation of a harmonised PL text**: Section 3.1 describes the initial harmonisation of PL content across the EU (within MRP countries). Two examples demonstrate the various approaches how to write the different sections of a PL in the past. The attempt is made to group relevant countries according to their perception of how the legal obligations of *Directive 92/27/EEC* can be met.
- **Diagnostic Leaflet Testing**: Section 3.2 outlines the consequences of these testing aspects, which have a direct or indirect effect on the PL. The direct impact comes from the actual answers given in the interviews or the PL review, whereas the indirect impact might emerge from the drafting of a questionnaire or the interpretation of pass mark criteria.
- **Impact on PL during MRP phase**: Section 3.3 gives examples of the comments of RMS and CMS on harmonised PLs and their test reports. The implication of these comments and requests is explained and a potential relationship to national attitudes outlined in section 3.1 is discussed.
- **Impact on PL during national phase**:Section 3.4 deals with the 'finishing' of PLs, i.e. the process to transfer the mutually agreed upon English PL text into the national versions of the local packaging. This step includes Blue Box Concept aspects and approval timelines.

3.1 Creation of a harmonised PL text

A widespread assumption, one might have, at first glance is that national PLs in the EU are quite similar to each other, particularly the ones from an established MRP product. This assumption is based on the European wide implementation of *Directive 92/27/EEC* into national law as well as based on more than 10 years of experience with harmonised PLs in CPs.

A serious approach to the creation of a harmonised PL text starts with the collection of the following documents:

- MRP-SPC of the respective product
- Annotated QRD template for decentralised procedures
- Nationally approved PLs of RMS and CMS countries

An obvious question to start with would be: What will be the impact **of** the already nationally approved PLs **on** the final harmonised PL?

However, two major points emerge quite clearly from the first steps in providing a harmonised PL text for an established MRP product:

- Nationally approved PLs vary a great deal. It is not suitable to merely take one of the existing PLs and adapt it with a few minor changes after briefly consulting the other national versions. Such attempts were to no avail and led to the insight that the appropriate strategy was to develop a new original version of the entire leaflet with the MRP SPC and the QRD template as guiding documents.
- The second obvious fact is that writing a PL can not be done by just following a best practice guide or after attending a three-day seminar.

> *'Professionally developing a prototype medicine information artefact requires integrated high level skills in writing, graphic design, and information design. Acquiring these skills takes training, time and practice.'*[65]

Obviously, the pharmaceutical companies as well as the CAs will tend to stick to *'their way, how it was always done'* as soon as it comes to nationally approved PLs. As a consequence, there is not so much an impact of existing national PLs **on** the prototype (i.e. the harmonised PL), but rather the reverse; i.e. a harmonised and mutually agreed upon PL would contain major changes when compared to the initially existing national PLs.

Obvious deviations emerge as soon as respective national PLs are directly compared to each other. Below, two examples are provided to demonstrate these country specific approaches. The first example (section 3.1.1), which is based on the various sections of a PL, shows how broad the presentation range is seen from the perspective of the SPC. The second example (section 3.1.2) also discussed the various sections of the PL and their different content, but the viewpoint is focussed on the perspective of the Western Europe countries.

3.1.1 Example 1 – PL sections vary

This example shows a harmonised PL drawn up for an established MRP product with only three countries concerned. Considering the sheer amount of information from a volume perspective leads to a picture that shows the discrepancies between the existing PLs and the proposed harmonised text (Fig. 7).

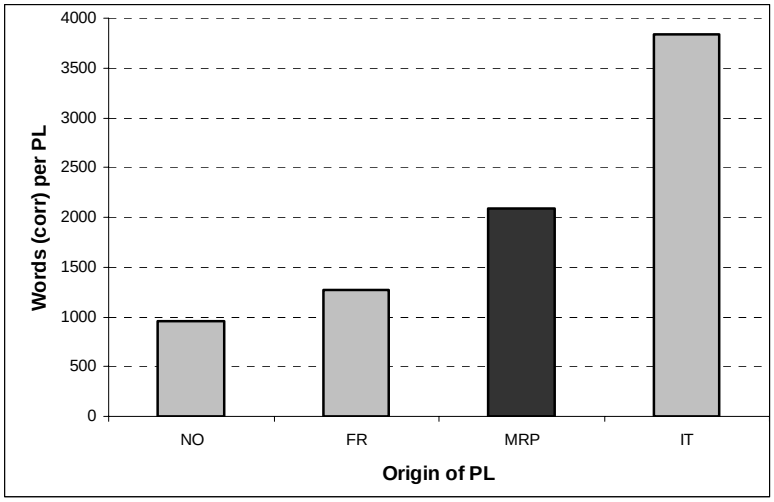

Fig. 7: The number of words of nationally approved PLs of three countries involved in a MRP (NO, FR, IT) is compared to a proposed harmonised PL (MRP) in English. The numbers were adjusted by a factor that takes into account that different languages need a different number of words to express the same amount of information. For corrective factors please refer to Appendix 1 (Tab. Appendix 1-3).

The impression might arise that the Italian version explains all issues at considerable length to patients, being comprehensible and patient friendly. However, it turned out that the Italian PL as the longest version is the most patient unfriendly one, as it is more or less the original text from the SPC that simply omits the section on pharmacology. This is fully consistent with the information in section 1.3 (Tab. 1) on the Italian approach for implementing PLs at the national level.

A closer look into the sections of these PLs reveals an uneven distribution of text used. Five sections that are deemed essential for the safe and effective use of a medicinal product were selected from the SPC level for further investigation at the PL level (Fig. 8): Contraindications (CI), Warnings and Precautions (W&P), Interactions with other medicinal products (IA), Posology (P), and Adverse Reactions (ARs);

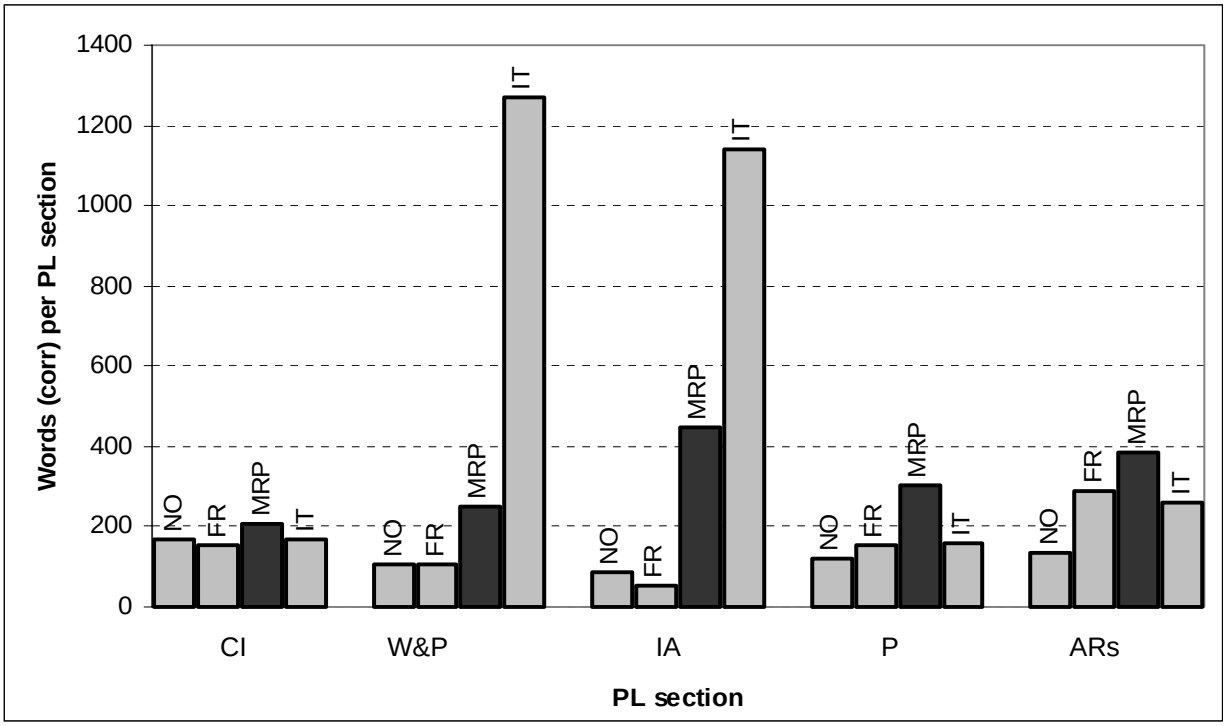

Fig. 8: The number of words per section in nationally approved PLs is compared to a proposed harmonised PL (MRP) in English. Countries involved in a MRP (NO, FR, IT) are shown in grey. Proposed harmonised PL (MRP) in English is shown in black. Sections are listed as follows: CI: Contraindications; W&P: Warnings and Precautions; IA: Interactions with other medicinal products; P: Posology; ARs: Adverse Reactions; The numbers were adjusted by a factor that takes into account that different languages need a different number of words to express the same amount of information. For corrective factors please refer to Appendix 1 (Tab. Appendix 1-3).

[87] The section on **Contraindications** is obviously the least susceptible to major differences (in the number of words) when it comes to transferring information from the SPC to PLs (Fig. 8, CI). A possible explanation for this might be that the consequence for a patient's action is quite simple in case of a contraindication. It simply is 'Do not take X'. No explanation is expected about the physiological conditions or pharmacological consequences when neglecting this advice. Consequently, a mere translation from medical terms into lay terms is necessary. As it generally requires more words in lay language to explain a medical term, the MRP text is a bit longer. For example if there are some '*hereditary*' diseases that lead to a contraindication, a proposal to express this in lay terms would lead to diseases, '*which run in the family*'.

[87] Symbol sign developed by AIGA ['No Entry'], http://www.aiga.org/content.cfm?ContentID=147

[88] The section on **Warnings & Precautions** shows the biggest discrepancy between the Italian SPC-like PL and the other PLs (Fig. 8, W&P). A possible explanation for this might be that in this section the most important thing is to make it clear to the patient in what circumstances and conditions he might be concerned about adverse consequences and what he could actually do in such situations. As in most cases it is the physician who must do or can do something, the task of the PL is to refer the patient to his/her doctor. There is no need to explain the physiological background or to give detailed medical instructions such as those in the SPC. The seriousness of the situation should be reflected by the time (before or during treatment) and the urgency (immediately or at once) the patient is advised to consult a doctor. The restriction to the mere mentioning of conditions and situations and the general advise to refer to the physician results in comparably short sections:

SPC: *'Elevated liver transaminases have been observed with X therapy. However, transaminase elevations were reversible upon discontinuation of X. Liver tests including AST and ALT must be performed periodically in all patients during therapy with X and prior to treatment in case of history and/or symptoms of hepatic dysfunction (e.g. jaundice, nausea, fever, and/or malaise). If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal, X must be discontinued.'*

PL: *'Take special care with X and tell your doctor if you have liver problems, which may cause your eyes or skin to go yellow (jaundice) or make you feel sick, have a high temperature (fever) and generally feel unwell. Your doctor may need to do blood tests either before or during treatment.'*

[89] The section on **Interactions** with other medicines is the most challenging one when it comes to providing a text that thoroughly explains to the patient all he needs to know about concomitant medication (Fig. 8, IA). The need here is to cover the appropriate interaction mechanisms in a patient friendly manner, without having endless lists of International Non-proprietary Names (INNs), which are possibly incomplete. The mere INN listing is often the case for existing PLs in Europe. However, this pure listing of active substances is of limited value for the patient since he does not grasp the underlying mechanisms of interactions. The patient must be enabled to deduce from a rough description of the pharmacological group or mechanism to the medication he currently uses, even if the latter is not listed with the INNs. In this section there is a need to have these two approaches running parallel. On the one hand an explanation of 'class effects' in lay language is necessary (if the whole class is affected) and on the other hand INNs and medical keywords, e.g. 'sympathomimetics' are needed for recognition in the 'other leaflet' by the patient.

This double approach, which is quite comprehensive leads to a text that is in most cases longer than it has been up to now in existing PLs. However, there is no need to go into detail of the physiological reactions or pharmacological effects that might arise. It should be made clear how big the impact of these interactions might be. Therefore different levels of urgency concerning the avoidance of these medicinal products, or instructions advising patients to see a doctor have to be provided by the PL.

[88] Road sign, used in the Austrian traffic system. http://commons.wikimedia.org/wiki/Category:Diagrams_of_road_signs_of_Austria?uselang=de

[89] No official symbol. Arrows indicate danger of collision.

SPC: 'Potassium-Wasting Drugs (e.g. (IV) amphotericin B, (systemic)gluco- and mineralocorticoids, tetracosactide (cosyntropin), stimulant laxatives): Increased hypokalemic risk (additive effect). Monitor and, if necessary, correct plasma potassium. This is particularly important when using Y concomitantly. Use nonstimulant laxatives.'

PL: 'Consult your doctor if taking X with any of the following medicines, because you may need special supervision: Medicines that may lead to loss of potassium, such as amphotericin B, corticosteroids, stimulant laxatives.'

[90] The section on **Posology** differs only slightly in its length within the various national PLs (Fig. 8, P). It is in most cases a straight forward description of when and how to take the medicine, accompanied by some advice for special patient groups, if necessary. However, as this is the only section in which people actually have to **do** something, particular attention should be paid to give an unquestionable description, sometimes referring back to the doctor.

SPC: 'If X therapy is discontinued for an extended period, re-institution of therapy must include a dose escalation.'

PL: 'If you have not taken X for some time and want to start it again, you must begin with a low dose. Please ask your doctor for advice.'

Surveys[104,106] show that this section is the one that patients are most interested in and get most frustrated about a PL if they can not find it at once. Considerations must be taken how to highlight this section, while still being in line with regulatory obligations. It is not possible to have it at the beginning of the PL, where most patients would like to see it, but it might be possible to fold a leaflet in such a way, that the posology section comes first when opening the package. Another approach discussed could be to highlight this section using colour or a different font size.

[91] The section on **Adverse Reactions** ('side effects' on PL level) shows quite a big difference in the example provided between the Norwegian PL and the other nations (Fig. 8, ARs). However, this in not due to the suspected incompleteness of the list of side effects in the Norwegian PL. There is a mere linguistic and text simplifying explanation. Obviously there are not as many words needed to describe certain side effects in Norwegian. Additionally, Norwegians seem not to be offended by the simplified wording used in the example. The English harmonised PL text was written by using proposals from MHRA or medical associations for translations of English medical terms into English lay language. The term 'conjunctivitis', for example, is translated with '*irritation and redness of the thin membrane covering the eye'*. This is terminology quite long winded, taking 10 words to explain one term. However, the translation 'pink eye' used in colloquial English, which would be on the level of the brevity of Norwegian text, is considered inappropriate as it has a slight slang connotation. In addition it might lead to unintended humour in the translations. On the other hand, in the search for a lay term for 'eructation' the UK assessor's proposal was to use 'burping' and his comment was: 'There is no need to be shy'.

⇒ At a first glance, the major effects that the harmonised PL proposal might have on the content of existing PLs are:

[90] No official symbol. Clock indicates time point(s) for taking the medicinal product.
[91] No official symbol. Non-smiling face indicates disadvantages for the patient.

- Omission of pharmacological details with no relevance to the actions a patient should be able to perform (→ shortening of PL length)
- Omission of treatment details only of relevance to the physician, e.g. in the section overdose (→ shortening of PL length)
- Introduction of explanations for classes of medicinal products mentioned in the section interactions (→ lengthening of PL)
- Replacement of medical terms by lay terms (→ lengthening of PL)

3.1.2 Example 2 – Country specific attitudes vary

In this example country specific practices of configuring the different sections within a PL are compared to each other. With the knowledge of these country specific approaches reactions from European affiliates during harmonised PL creation or from CAs during harmonised PL assessment become more comprehensible (section 3.3 *Impact on PL during MRP phase*).

Non-harmonised PLs from a common MRP 'prescription only product' serve as an example. The sections are analogous to Indication (I)/What X is used for, Contraindications (CI), Warnings and Precautions (W&P), Interactions (IA), Posology (P), and Adverse Reactions (ARs). They were considered as the most crucial ones for safe and effective use of this product. Fig. 9 shows by country the number of words assigned per section.

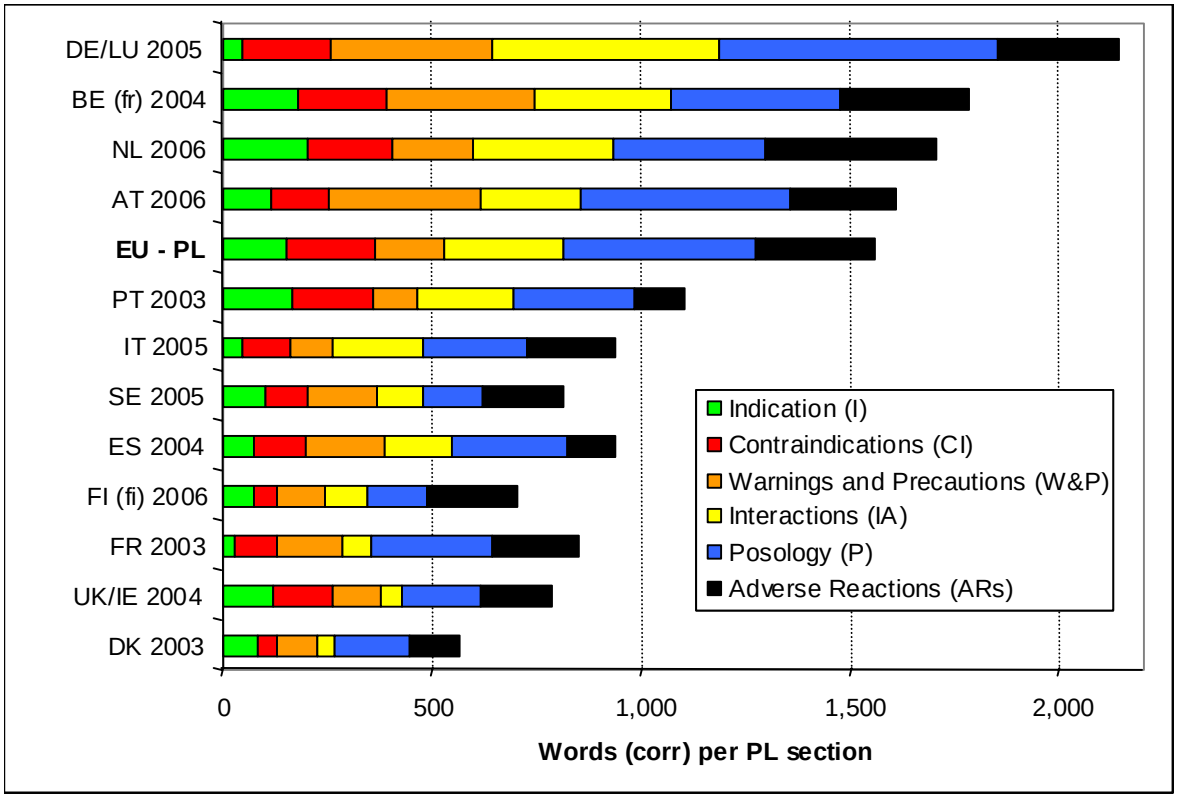

Fig. 9: Nationally approved PLs from 14 EU countries involved in a MRP. The text amount needed for the sections I (green), CI (red) W&P (orange), IA (yellow), P (blue), and ARs (black) is presented. The numbers were adjusted by a factor that takes into account that different languages need a different number of words to express the same amount of information. For corrective factors please refer to Appendix 1 (Tab. Appendix 1-3). Countries are displayed according to ISO 3166[92]. For BE and FI the language version used is indicated in brackets. 'EU-PL' indicates the harmonised version according to QRD template. Text concerning pregnancy and lactation, storage, or further information on administrative issues was not broken out separately, but was included within the numbers for total text. This information is not shown in the graph However, countries were sorted in descending order by the volume of their total text.

[92] http://www.iso.org/iso/en/prods-services/iso3166ma/02iso-3166-code-lists/list-en1.html (accessed 3.1.2007)

On these raw data a further evaluation was performed. A country specific assessment of the percentage of text per section in relation to the overall PL is shown in Tab. 7. Additionally, a review of content revealed country specific differences and an attempt was made to categorize these specific approaches. Furthermore, the relationship to recommendations from the annotated QRD template is shown. Conclusions were drawn concerning which categories would already be in line with QRD templates and which would have to extend or decrease the information they give to fall in line with the European perception of an adequate PL.

Tab. 7: Non-harmonised, nationally approved PLs from a MRP product are listed according to increased overall words (W) per leaflet. The total amount of words per section and its percentage of the whole PL text are displayed in columns. Sections are listed as follows: I: Indications, CI: Contraindications, W&P: Warnings and Precautions, IA: Interactions with other medicines, P: Posology; ARs: Adverse Reactions The numbers were adjusted by a factor that takes into account that different languages need a different number of words to express the same amount of information. For corrective factors please refer to Appendix 1 (Tab. Appendix 1-3). Bold print indicates the max. and min. within one PL-section. Colours represent the groups to which the countries were assigned section wise in the text below this table.

Country	Total	I		CI		W&P		IA		P		ARs	
	W	W	%	W	%	W	%	W	%	W	%	W	%
DK	809	83	**11.2**	48	5.9	92	11.4	43	5.4	178	22.0	228	14.7
IE / UK	1124	121	10.8	140	**12.5**	116	10.3	51	**4.5**	189	16.8	168	14.9
FR	1206	29	2.4	97	8.1	159	13.2	70	5.8	287	23.8	207	17.2
FI (fi)	1225	75	6.1	51	**4.2**	117	9.5	101	8.3	142	11.6	218	17.8
ES	1285	73	5.7	124	9.7	190	14.8	159	12.4	275	21.4	117	9.1
SE	1339	100	7.5	103	7.7	164	12.3	108	8.1	146	**10.9**	192	14.3
IT	1538	44	2.8	117	7.6	101	**6.6**	215	14.0	249	16.2	210	13.6
PT	1602	166	10.4	192	12.0	108	6.8	227	14.1	292	18.2	119	**7.4**
EU	1992	152	7.6	210	10.5	165	8.3	284	14.3	459	23.1	285	14.3
AT	2120	115	5.4	139	6.6	359	**16.9**	241	11.4	499	23.5	255	12.0
NL	2205	202	9.2	204	9.3	193	8.7	335	15.2	362	16.4	410	**18.6**
BE (fr)	2504	181	7.2	210	8.4	353	14.1	327	13.1	401	16.0	310	12.4
DE / LU	2729	44	**1.6**	213	7.8	385	14.1	543	**19.9**	664	**24.3**	291	10.7

[93] **Indication / What X is used for**

This section is generally of little interest to the user of 'prescription only medicines' in terms of supporting his decision, as the decision whether the medicinal product is the appropriate one was already taken by the physician. However, this section is highly appreciated by patients seeking general information about their medication and / or disease. Regarding the kind of information provided, three groups of countries can be distinguished:

1. **No explainer** (Indication): These countries (FR, IT, DE/LU) provide as little information as possible. They only mention the indication(s) that are stated in the SPC and do not attempt to put the indication in the context of the patient. Amongst these countries some take the opportunity to have a patient friendly wording (FR, IT) whereas others try to give a quite complete and correct statement of the indication similar to the SPC wording (DE/LU).
2. **Medium explainer** (Indication / working mechanism): These countries (FI, ES, IE / UK, SE, DK) at least take the effort to explain the working mechanism of the INN in addition to the indication.
3. **Full explainer** (Indication / working mechanism / disease): These countries (AT, BE, NL, PT) make an effort to explain to the patient the indication in a manner that also presents the working mechanism of the INN as well as the nature of the disease or its

[93] Symbol sign was developed by AIGA 'Exit', http://www.aiga.org/content.cfm?ContentID=147

symptoms which will be cured or treated. In effect, they try to present the 'whole' picture of the patient's situation.

The annotated QRD template[94] expects the MAH to describe the '*pharmacotherapeutic group or type of activity*' using patient understandable language. Therefore, the **Medium explainer** countries would already be in line with their approach, whilst the No explainer countries would have to achieve this status in the future.

The section on indication(s) is the only section where MAHs can describe some of the positive properties of the medicinal product (i.e. curing or preventing a disease or symptom) without being immediately blamed for having incorporated promotional statements. To enable the patient to do a proper risk-benefit analysis, MAHs must take this opportunity to also clearly state the positive aspects of the medicinal product.

[87] **Contraindications**

This section is of little interest to the patient in the case of 'prescription only medicines'. All possible contraindications should have been evaluated by the physician before doing the prescription, and most patients 'trust' in their doctors to have considered it appropriately. There are three groups that can be distinguished:

1. **Reducer** (Simplification / grouping): These countries (FI, SE, IE/UK, DK) group the different contraindications of the SPC into a few general terms that literally comprise more than the original SPC statements from the scientific point of view. However the grouping results in fewer items stated in the PL than in the SPC.
2. **Disclaimer** (Full disclosure / No explanation): These countries (FR, IT, ES) merely transfer the contraindications listed in the SPC to the PL, paying little attention to whether they would be understood by the patient. There is no effort made to explain the terms or to simplify and group them for better understanding.
3. **Explainer** (Full disclosure / Full explanation): These countries (DE/LU, NL, BE, AT, PT) have a literal translation of the terms from the SPC into patient understandable language. This leads to as many items as are mentioned in the SPC. The text is longer, because the translation into patient understandable terms needs more words.

The annotated QRD template[94] expects the MAH to describe the contraindications in accordance with the SPC and explicitly asks to '*ensure that complex details are **not** omitted*'. In addition, a full disclosure is obligatory as it is '*not acceptable to state only common or major contraindications*'. As a patient understandable language is required, only the **Explainer** countries are already in line with their approach. All other countries would have to achieve this status in the future.

[88] **Warnings & Precautions**

This section is of great importance for the user of a 'prescription only medicine'. This is because it contains the instructions to patients/users concerning how to act in various situations. Some conditions are already present at the time of prescription. Threfore the prescribing physician should have taken them into account to allow the patient to rely on his physician's decision. However, some conditions are not foreseeable and may occur during treatment. If they do arise it will be the patient who has to decide what to do, ideally acting appropriately according to the PL's instructions. There are three groups that can be distinguished:

[94] http://heads.medagencies.org/mrfg/docs/pi/QRD_annotated_template_CMDh.pdf (October 2006)

1. **Concealer** (No full disclosure concerning patient's actions): These countries (FI, DK) restrict the information provided to the keywords of the concerned diseases. There is no mention of certain categories of users such as children or the elderly
2. **Basic performer** (Full disclosure concerning patient's actions): These countries (IE/UK, ES, SE, PT, NL, IT, FR) also restrict the information provided to keywords of the concerned diseases, but concomitantly give advice to contact the doctor in the respective situations. No explanation is given for the underlying reason for or specific advice on what the doctor might do. There is no mention of certain categories of users such as children or the elderly
3. **Comprehensive performer** (Full disclosure as in SPC): These countries (DE/LU, BE, AT) include all items mentioned in the SPC in the PL, using lay terminology. They also provide detailed advice on the doctor's actions in specific situations. Certain categories of users such as children or the elderly are focussed on and a patient friendly terminology is used.

The annotated QRD template[94] expects the MAH to provide special warnings and appropriate precautions. In addition, it is expected that the particular conditions of certain categories of users as well as special patient populations are taken into account. However, as there is no explicit statement that it has to be in concordance with the SPC, there is some room for interpretation on the extent of description needed. Certainly, a detailed description of the physician's action for specific situations can be easily omitted as long as the remaining text ensures that the user contacts his physician in critical situations. Therefore, the **Basic performer** countries (Full disclosure concerning patient's actions) countries are those, which are almost meeting current expectations. However, all of them failed to mention certain categories of users, and most of them could improve patient friendliness by explaining medical terms in lay language.

[89] **Interactions**

This section is of particular importance for the patient, even in case of 'prescription only medicines', where the physician should have considered potential interactions prior to prescription. At the same time this is one of the most complex sections to be understood by a patient since it deals with a range of pharmacotherapeutic groups and action mechanisms of various medicinal products. There are three ways to cope with this situation that can be identified:

1. **Pointer** (Reference to the doctor): These countries (IE/UK, FR, DK) simply state that in case any other medicinal products are consumed (even those not prescribed) the doctor needs to be consulted. IE / UK do not mention any INN, but just roughly describe a few therapeutic areas in general terms as examples (such as 'medicines to treat diabetes', 'cough medicines'). FR and DK defer as well to the doctor, but do mention in the PL in general terms the medicinal products that are listed under 'contraindicated' or 'not recommended' in the SPC. However, all other medicinal products or pharmacotherapeutic groups of the SPC are completely left out.
2. **Disclaimer** (Reference to the doctor / List of therapeutic areas with INNs): These countries (FI, SE, ES, NL, BE, AT) give a complete list of the therapeutic groups concerned and specify them by giving INNs as examples. Overall, this approach might not be comprehensive enough for the patient. However, he has more possibilities to find out if he has to be cautious about taking certain medicines. This is because he can at least compare the INNs with PLs of other medicinal products he is taking at the same time. Depending on how short (FI, SE, ES) or how long (NL, BE, AT) the explanations of the different therapeutic groups are the patient will be able to recognise if he should be concerned, even when his other medicine's INN is not explicitly listed.

3. **Explainer** (Reference to the doctor/ List of therapeutic areas with INNs / Explanation how the effect is affected): These countries (PT, IT, DE) try to explain in addition to the information what therapeutic groups are concerned, what the effect might be in case of concomitant use of other products, such as decreased or increased effect of the medicinal product.

The annotated QRD template[94] expects the MAH to '*describe the effect of other products on the product in question and vice versa*'. Reference to weakening / intensification or shortening / extension of effects is expected. Even if not explicitly stated that this section has to be in accordance with the SPC, it is obvious that **all** interactions that are mentioned in the SPC have to appear in the PL. Additionally, the description of the effects is requested. Therefore the **Explainer** countries are those that are in line with current requirements, and the others will have to amend their national texts substantially.

[90] **Posology**

This section is the most interesting one from the patient's perspective. In surveys[50,106] patients often claim to be solely interested in '*when to take how much*' of the medicine, and therefore they recommend this section be placed at the very top of the PL.There are three approaches how countries display the desired information:

1. **Non-performer** (Restrictive information / Deferral to the doctor): These countries (SE, FI, IE/UK) merely have a few very common statements on posology. The only distinctive information given is the amount of maximum recommended dose and the phone number of the poison centre (SE, FI). There is no information provided about statements from the SPC such as the normal daily dosage or on special patient groups such as children, the elderly, or patients with reduced kidney or liver functions. The English PLs (IE/UK) strictly refer to the doctor for '*amounts of tablets when to take'*, but they do give some general core information on what to do when a dose is missed or what happens if treatment is stopped abruptly (see Basic performer).
2. **Basic performer** (Full information for 'standard' posology / Additional information for the patient): These countries (BE, NL, IT, PT, ES, FR, DK) provide the complete information on the 'usual' dose. They also give information to the patients that is not described in the SPC, since it is self evident for physicians. Examples are: '*What to do if a dose was missed'*, '*what happens if treatment is stopped*'. This is information that makes the difference between PLs and SPCs and is strongly promoted by the QRD templates.
3. **Full disclosure performer** (Full information in analogy to SPC / Additional information for patient): These countries (DE/LU, AT) give full information on the SPC to their patients, including recommendations on special patient groups such as children, the elderly, or patients with reduced kidney or liver functions. These countries, being in full concordance with the SPC also provide information that is only valuable for the physician.

The annotated QRD template[94] expects the MAH to describe the (standard) dosage and the method of administration. The description of the frequency of administration or the duration of treatment is only provided if appropriate. However, in addition to the corresponding section 4.2 in the SPC in the '*How to take X'* section of the PL, patient relevant information on overdose is also requested. Besides that the QRD template requires additional instructions for the patient on what to do if a dose is missed, as well as additional information about what happens if treatment is stopped. As a consequence, the approach of the **Basic performer** countries is in line with the QRD templates. **Non-performer** countries that defer even for

information on standard posology to the physician will have to change their national approach in a substantial way.

[91] **Adverse Reactions**
Most patients are strongly interested in this section. At the same time this section is the main reason for incompliance, stopping a treatment or not starting a treatment at all. The length of this section and the fact that it often is a full reflection of the corresponding SPC section is due to the 'strict liability system' that governs responsibility for damages caused by products in Europe. There are four approaches of displaying the side effects that were used before QRD templates for MRP products became available and mandatory:

1. **Hiding** (No full disclosure of ARs / No quantification of frequencies): These countries (IE/UK, ES, PT) do not list all side effects according to the SPC. They group several side effects under one very general term or they omit side effects that cannot be noticed by a patient, such as changes in blood parameters. The differentiation on frequencies is only provided on a qualitative level, using words such as 'common', 'menos frecuentes', 'uncommon', 'mas raramentes', and 'rare', but not on a quantitative level.
2. **Listing** (Full disclosure of ARs / No quantification of frequencies): These countries (FR, DK) list all side effects according to the SPC and give explanations of medical terms. In the PL only qualitative differentiations are made, despite the availability of quantitative data for the side effects in the SPC.
3. **Disclaiming for Patients** (Full disclosure of ARs / Quantification of frequencies): These countries (SE, IT, FI) list all side effects according to the SPC and also the frequency terminology is explained on a quantitative basis for the patients. The side effects are sorted according to the frequency group, which results in three to four subsections.
4. **Disclaiming for Physicians** (Full disclosure of ARs / Quantification of frequencies / Sorting to SOC (System Organ Class)): These countries (AT, NL, BE, DE/LU) give full information on side effects, as displayed in the SPC, including the grouping of side effects on the first level according to SOCs and on the second level according to frequencies.

The annotated QRD template[94] expects the MAH to describe the side effects (Adverse Reactions), including the frequencies according to MedDRA (Medical Dictionary of Regulatory Affairs), which means that frequencies should be quantified. Therefore, the approach of the **Disclaiming for Patients** countries is the one that currently best reflects the requirements of QRD templates. It is not explicitly forbidden to sort frequencies according to SOCs but in case this approach is chosen, it has to be ensured that the terms are appropriately translated to be patient understandable. The disadvantage of SOC displaying are formal ones: Firstly, there is more text (SOCs and repetition of frequency terms per SOC) and secondly, there are more subsections, making the PL less transparent.

⇒ All these country specific attitudes towards the various sections of PLs in the past have to be levelled out in the harmonised PLs. The impact on some of the national PLs is therefore substantial, whilst for others not.

3.2 Impact on PL by Diagnostic Leaflet Testing

During the performance of PL-testing, particularly during Diagnostic Leaflet Testing, there are several steps taken which have an impact on the PL. In general, even when outsourced to a CRO, the MAH is deeply involved in the discussions related to the testing of the PL. The most important steps, when feedback from the MAH is required, are:

- Review of PL by CRO
- Creation of mock-up
- Pilot testing
- First round of interviews
- Second round of interviews

} Direct impact on PL

Additionally, there is input from the MAH needed for the following parts of the testing procedure:

- Creation of questionnaire
- Decision on further round(s) of interviews
- Final report on PL-testing

} Indirect impact on PL

In the following sections these steps and their impact on the PL are elaborated on in more detail. The first part about the direct effects (section 3.2.1) is naturally structured by three key aspects:

- Revision by the CRO and answers to specified questions (section 3.2.1.1)
- Answers to general questions (section 3.2.1.2)
- Design of PLs (section 3.2.1.3)

The second part about the indirect effects (section 3.2.2) focuses on the questionnaire and the finalisation of the test (i.e. the decision on success and the final report).

3.2.1 Testing steps with direct impact on PLs

As mentioned above, there are several steps during Diagnostic Leaflet Testing that lead to changes in the PL. In general, the most significant changes occur in the internal **PL review procedure of the CRO**. This is mainly a text review by experienced people. They remove difficult text passages, which they predict would fail in personal interviews, and replace them with passages that are more patient friendly. Some CROs support this internal step by one or two **interviews with expert patients.** By this latter approach the questionnaire is pre-tested as well. Besides necessary re-wording, some rearranging of the text is often proposed by the CROs. The purpose of this step is to eliminate duplications or to group by similarity of statements.

However, the experience with four different CROs so far has shown that it is of utmost importance for the MAH to be deeply involved in the discussions and to prevent the scientific content of the PL to deviate from the SPC, which may result from ‘better’ or ‘simpler’ wording, or by wrongly assigned statements during re-arrangement processes. ‘Final release’ by the MAH for every PL version of the different testing steps is a useful approach.

To better demonstrate this procedure three Diagnostic Leaflet Tests were evaluated for changes of the proposed harmonised PL text. In the following changes due to CRO’s PL check, a potential pilot test, and the first and second interview rounds are described.

3.2.1.1 Revision by CRO and answers to specified questions

Three PLs of medicinal products (A, B, C) were used as examples to show the impact on PLs of the different steps in Diagnostic Leaflet Testing. The number of words was chosen as the parameter to demonstrate changes on a quantitative basis. Calculations on products A (Tab. 8) and B (Tab. 9) show that most changes in the PL text occur in the steps **before** the first

interview round is started. The outcome of the first and second round of interviews only leads to minor revisions of the PL.

Tab. 8: Quantitative aspect of changes on harmonised PL text for Product A due to the various steps during Diagnostic Leaflet Testing. The outcome PL text version of the respective step was set as 100 %, then calculations were performed for the percentage of text unchanged (Orig.), the percentage of text added (New), and the percentage of text deleted (Del). The figures for the *Revision by CRO* are based on their initial revision proposal. Subsequent discussion of the final wording with the MAH was not considered. Rearranged text is covered by the categories 'New' and 'Del'.

Product A						
Step during Diagnostic Leaflet Testing / Section of PL	**Revision by CRO**			**Two interview rounds**		
	Orig. %	**New** %	~~Del~~ * %	**Orig.** %	**New** %	~~Del~~ ** %
1 What X is …	**73**	**10**	~~17~~	**90**	**10**[1]	-
2 Before you take X						
Contraindications	**79**	**16**	~~5~~	**100**	-	-
Warnings & Precautions	**83**	**10**	~~7~~	**100**	-	-
Interactions	**29**	**39**	~~32~~	**100**	-	
3 How to take	**94**	**5**	~~1~~	**95**	-	~~5~~ [1]
4 Possible side effects	**72**	**15**	~~13~~	**100**	-	-
5 How to store	**100**	-	-	**100**	-	-
6 Further information	**100**	-	-	**100**	-	-

* Text used as the basis for calculation of percentages was the initial text in a tracked changes mode.
** Text used as the basis for calculation of percentages was the revised text in the tracked changes mode.
[1] Changes are due to moving a statement of 21 words from section 3 to section 1 after the second test round. After the first test round part of this statement was highlighted using bold print.

Tab. 9: Quantitative aspect of changes on harmonised PL text for Product B due to the various steps during Diagnostic Leaflet Testing. The outcome PL text version of the respective step was set as 100 %, then calculations were performed for the percentage of text unchanged (Orig.), the percentage of text added (New), and the percentage of text deleted (Del). The figures for the *Revision by CRO* are based on their initial revision proposal. Subsequent discussion of the final wording with the MAH was not considered. Rearranged text is covered by the categories 'New' and 'Del'.

Product B									
Step during Diagnostic leaflet testing / Section of PL	**Revision by CRO**			**Pilot testing**			**Two interview rounds**		
	Orig. %	**New** %	~~Del~~ * %	**Orig.** %	**New** %	~~Del~~ ** %	**Orig.** %	**New** %	~~Del~~ %
1 What X is …	**66**	**22**	~~12~~	**100**	-	-	**100**	-	-
2 Before you take X									
Contraindications	**94**	**2**	~~4~~	**88**	**5**	~~7~~	**100**	-	-
Warnings & Precautions	**53**	**27**	~~20~~	**89**	**2**	~~9~~	**100**	-	-
Interactions	**94**	**3**	~~3~~	**26**	**33**	~~41~~	**100**	***	-
3 How to take	**91**	**7**	~~7~~	**90**	**3**	~~7~~	**100**	-	-
4 Possible side effects	**84**	**11**	~~5~~	**96**	**1**	~~3~~	**100**	-	-
5 How to store	**56**	**44**	-	**100**	-	-	**100**	-	-
6 Further information	**96**	**1**	~~3~~	**90**	**5**	~~5~~	**100**	-	-

* Text used as the basis for calculation of percentages was the initial text in a tracked changes mode.
** Text used as the basis for calculation of percentages was the revised text in the tracked changes mode.
*** Underlining of two subheading after first test round.

However, calculations for product C (Tab. 10) show that even after an initial PL check by the CRO the interview rounds lead to further changes of the PL.

Tab. 10: Quantitative measurement of changes on harmonised PL text for Product C due to the various steps during Diagnostic Leaflet Testing. The outcome PL text version of the respective step was set as 100 %, then calculations were performed for the percentage of text unchanged (Orig.), the percentage of text added (New), and the percentage of text deleted (Del). The figures for the *Revision by CRO* are based on their initial revision proposal. Subsequent discussion of the final wording with the MAH was not considered. Rearranged text is covered by the categories 'New' and 'Del'.

Product C									
Step during Diagnostic leaflet testing / Section of PL	**Revision by CRO**			**First interview round**			**Second interview round**		
	Orig. %	New %	~~Del~~ * %	Orig. %	New %	~~Del~~ ** %	Orig. %	New %	~~Del~~ %
1 What X is …	98	2	-	100	-	-	100	-	-
2 Before you take X									
Contraindications	100	-	-	100	***	-	65	12	~~23~~
Warnings & Precautions	60	12	~~28~~	68	16	~~16~~	100	-	-
Interactions	67	17	~~16~~	99	1	1	91	7	~~2~~
3 How to take	82	10	~~8~~	100	-	-	100	-	-
4 Possible side effects	98	1	~~1~~	72	14	~~14~~	100	-	-
5 How to store	100	-	-	100	-	-	100	-	-
6 Further information	100	-	-	90	5	~~5~~	100	-	-

* Text used as the basis for calculation of percentages was the initial text in a tracked changes mode
** Text used as the basis for calculation of percentages was the revised text in the tracked changes mode
*** Capitalising of subheading after first test round

Analyzing the changes from a content perspective there are three groups or types that can be differentiated

- **Re-wording** of statements using different expressions and words that are presumably better understood by patients (Type 1).
- **Re-arrangement** of wording, i.e. using the same words, but ordered differently within a statement, or sorting statements in a different sequence, or bulleting statements etc. (Type 2).
- **Highlighting** single words or statements for greater emphasis by means of using bold type, underlining, or capitalising (Type 3).

Initial revisions of CROs (**before** test rounds) generally fall under type 1 (re-wording) or type 2 (re-arrangement). So far, all recommendations for type 3 (highlighting) have been based on the fact that the answer to one of the questions in the interview rounds could not be found. Even if the next test round performs better after highlights were made, this way to 'cure' the PL has to be thoroughly thought through, as there might be the danger of only curing one specific symptom (i.e. one statement), but neglecting the basic problem that leads to other incomprehensible statements that were not the subject of the question.

3.2.1.2 Impact on PLs triggered by answers to general questions

Interview protocols of CROs close with approximately three general open questions aimed at learning about the general impression the interviewee had on the PL. This is the second aspect leading to PL changes due to the interviews in the Diagnostic Leaflet Testing process. These questions were meant to serve as a 'chill-out' for the interview. The type of these questions is very different from those used for the diagnosis of the PL, since they belong to

the kind of questions used in attitude and opinion surveys. In most cases the answers are not specific enough to lead to a definite change in a particular word or sentence. Further as the individual comments within a group of tested people are quite often contradictory, it is difficult to derive from the answers/information received what changes the patients as a whole really would benefit from.

As previously mentioned, these general and open questions are not meant to generate measurable results in terms of pass mark criteria. This aspect and the unsystematic nature of responses tempt many CROs and MAHs to neglect these 'data'. However, all comments and answers to general questions should be taken seriously. This need is indicated by the assessment criteria of the MEB, which explicitly asks for these questions (Appendix 3). In addition, experience shows that the CAs sometimes cite single statements from the report and use them as a rationale to justify the objections made by the authorities.

The comments on five PLs indicate that there are three main topics that are always raised:

Length of PL – Amount of text: None of the persons interviewed complained about the PL being too short or giving too little information. On the contrary, only comments criticising the PL as being too long were received. Some examples may illustrate this perceived problem:

- *'Book format puts you off, would prefer a one page leaflet.'*
- *' … might be better as a booklet.'*
- *'Too long to be useful'*
- *'It does seem a lot to read for someone who is not very well'*
- *'Could put some people off as it looks like a lot of writing'*
- *'Too much information'*
- *'It was too detailed, too long, information overload. If I got the leaflet I wouldn't read it.'*
- *'The longer the leaflet the stronger (= more dangerous) is the medicine.'*
- *'... the print is quite small, but if you make the print bigger then it will have more pages. You can't cut down the text, because you are probably legally obliged to have it all.'*

Emphasising the important parts: As a consequence of having excessively long PLs interviewees automatically attempt to find a way of picking out the important points. Some propose to move the important information items to the top of the leaflet or highlight them in bold print. In general, for most respondents there is no question that it is likely not the whole PL that is important for them. Some examples may illustrate this:

- *'Dosage should be on the front page.'*
- *'… put … side effects at the beginning'*
- *'… administration should have been above the duration of treatment.'*
- *'It's not riveting reading'*
- *'I think the information people want to know first is how to take it, when to take it, what the side effects are, other stuff they'll read later. Some people miss valuable information, because there is a load of blurb first.'*
- *'I wouldn't go through it as much, just the side effects because I'd trust the doctor.'*
- *'My personal suggestion would be limiting this information to the most important things, the 'ought to know' in bold print, so they don't have to spend a lot of time searching.'*
- *'… If there was a gap between the sections, it'd be less mind numbing. … Also colour coding or different shades for important information.'*

Wording used: Comments on wording are most heterogeneous. There are as many positive opinions for well worded PLs with good explanations as there are complaints about the use of too many medical terms. These comments reflect the heterogeneity of the health literacy of people tested. It is particularly difficult to get people to understand that it might not be the

goal in every case that they understand every single bit of the PL. In some instances it might be the intention of the PL to make people recognise some information (e.g. an INN in the interactions section). Even when they do not understand the pharmacological aspect they could act appropriately by telling their doctor that they take such medication. Some examples may illustrate the heterogeneity of comments on the wording used in PLs:

- *'Too many medical terms.'*
- *' … some words, such as fever, not everyone will know what it means.'*
- *'Very gobbledegook.'*
- *'It's fairly easy to read.'*
- *'How does Joe Public know what [INN] derivatives are?'*
- *'I thought it was very good (language), you can understand it without being a medicine student.'*
- *'Have it less medical jargon to improve readability.'*

On the one hand these statements might be a source of valuable information about what the patient really needs, appreciates, misses or would prefer to change. On the other hand, due to the inconsistency and partly contradictory nature of the suggestions there is no clear-cut solution that would resolve all of these problems. The few distinctive complaints which are consistent, such as those concerning the overall length of PLs can not be 'cured' because of regulatory and liability constraints.

⇒ In summary, a test person's answers to these general open questions on the content and wording do not lead to a substantial change of the PL in the actual testing process.

3.2.1.3 Impact on PL design

Overall, there is very little change of the design of PLs due to Diagnostic Leaflet Testing. Most pharmaceutical companies have developed over years a so-called 'house-style'. This means they use a certain font type, format (portrait or landscape), number of columns per page, layout of title and headings, placing the company's logo, (etc.). The marketing unit of each company is interested in changing the PL design as little as possible in order to be still 'in line' with other printed public material produced by or for the company.

The overall conclusion about the impact of Diagnostic Leaflet Testing on PL design shows that there is some effort taken whilst creating the first mock-up of the PL for pilot testing or the first interview round. This effort consists mainly of choosing a font size, which is as big as possible and still workable, but never 12 pt or larger. In addition, within the scope of the 'preset' house style minor improvements are made towards producing a clearer structure by using bolded headings and bulleted lists.

However, the missing 'revolution' in PL design is not only due to the reluctance of companies to change their established 'house style'. It is mainly because of technical constraints for colour printing and size of PLs, or the heterogeneous acceptance by patients and CAs (please refer for details to section 2.7. *Technical considerations*).

Comments from interviewees on the proposed design of PLs are as varied as the ones on the content (section 3.2.1.2 above). Examples of comments on a black and white two-column PL, printed on A4 paper with 8.5 pt font and bold headings, are listed below:

- *'Could be A4[95] size rather than A3.'*
- *'Could have as a booklet form. A3 size too big. '*
- *'It's well set out. Has bullet points which help. Not too bad considering the size of the leaflet. It has good headings and things in bolder type which helps. Nice in columns rather than straight across.'*
- *'Good size print.'*
- *'Well laid out, not a bulky leaflet. Not having it so tightly spaced together would help. E.g. spread columns out a bit more, it dances in front of your face.'*
- *'More sections and headings to make it clearer. Subdivide if possibly and highlight, there is too much to wade through.'*
- *'Use larger print for elderly people.'*
- *'Use more tables.'*
- *'… the colour is depressing, … , add diagrams (to visualise things) for when to take in.'*

Font size, bold print, bullet points and headings are amongst the most debated design parameters of PLs. As a consequence of these general comments, particularly the ones mentioned above (section 3.2.1.2), complaining about lengthy PLs and asking for better navigability, these aspects are intensively discussed at pharmaceutical companies.

However, during the testing procedure only minor changes of the design are proposed by CROs. These proposals are all due to missed pass marks of single questions and aim at highlighting specific information that was not found by the interviewee (section 3.2.1.1). So far, no major changes have ever been proposed due to the comments made in response to the general questions.

In particular, the font size of tested PLs is limited for practical reasons. Average PLs of 2,000 words do not turn into better PLs if font size is increased from 8.5 pt to 12 pt. It would have the opposite effect, when the patient's perception of longer PLs is that the medicine is more dangerous.[96]

Beyond the statements made above the reason for the limited impact on PLs also lies within the lack of clear recommendations and examples which would undoubtedly improve the PLs and are their overall acceptance by authorities. Up to now, CAs in Europe did not come up with recommendations for overall PL design templates. There was an approach by the ABPI in the UK in 1988[97] suggesting a common layout but this would not be applicable to the QRD templates and the amount of information needed at present. A similar situation applies for the three different layout-proposals the FDA recently suggested.[98] The CRIA in Australia suggested a common layout for Australian products, which is marked by a newspaper style using several columns as well as **printing text passages in bold where the patient has to do something**.[15] Interestingly, most Australian companies use this style on a voluntary basis, indicating its general acceptance and usefulness. However, the application of this format to the European languages would probably be particularly problematic with languages that have much longer words compared to the English language.

A partial approach how to achieve a EU-wide common position, specifically for pictograms, is discussed further below (section 4.5 *Future of European PLs*).

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[95] This is **not** a typing error.
[96] Comment received during one of the testing procedure.
[97] ABPI: Patient information: Advice on the drafting of leaflets, 1988
[98] FDA. Guidance Useful Written Consumer Medication Information (CMI); July 2006

3.2.2 Testing steps with indirect impact on PL

Questionnaires used in Diagnostic Leaflet Testing are 'tailor-made' per product tested. This is one of the major differences compared to other methods for PL-testing, when standardized questionnaires are used that often just call for check marks (rather than essay type answers).

The development of the questionnaire rests upon some important ambiguities. A broad range of people concerned think that achieving the pass marks of a Diagnostic Leaflet Testing does not so much depend on a well-written, compiled, and designed PL, but rather on a questionnaire asking the 'right' questions. Therefore, CROs often put their efforts into drafting the questions rather than adapting a PL in a way that any question asked will be correctly answered. However, drafting and compiling the questions might be a very good opportunity to rethink the PL and answer for oneself the main question: 'What does the company want people to be able to do with this PL?'

According to the initial intention of the diagnostic testing of usability[15,22] the main thing to find out is, if people can actually **use** the PL. However, as the interviewed people are not in the real world of taking that medicinal product, their actions in specific situations (e.g. overdosing or experiencing a side effect) can not be observed. To solve this situation a surrogate is used in a manner that people have to describe the fictitious actions they would perform in case of the situation the question suggests.

When a questionnaire shows that the people can *easily use* the PL, the major requirement of *Directive 2001/83/EC as amended* Art 59 (3) '*… to ensure that it is legible, clear and easy to use'* is fulfilled. This is because the first two conditions of 'readability' and 'comprehensibility' are somehow prerequisites for 'easy use' of the PL.

There are a few technical hints given in guidelines[15,17] concerning the questionnaire:

- The wording should not be too simplistic (no repetition of keywords).
- The order of the questions has to be random.
- Most important safety issues have to be covered.

The experience with questionnaires shows that it is extremely important to ensure that only one question is asked at a time. The danger of double questions such as '*What are the symptoms of overdose and what should you do if you experience them?*' is that people start answering the first (or last) part of the question and forget the other part of the question. Therefore, any 'and' within questions should be examined critically and reconsidered. It is also very important to avoid using 'not' in questions if respondents have to answer 'yes' or 'no'. This is because a 'not' can lead to double negatives, which tend to cause confusion.

A general, self-evident requirement is the consideration, whether the respondent will understand the wording of the question. Any slang, cultural specific, or highly technical words must be avoided. Particularly the last point mentioned about the choice of words and the construction of questions will 'backfire' on the content of the PL if one earnestly tries to answer the questions posed from the perspective of a potential respondent. At that occasion it is often discovered that the PL is written in a style that is too complicated and does not allow for an easy response to the question. As a consequence a particular part of the PL may be re-written. In case the reason for the difficulties is a general one, repeated throughout the PL, the change induced by revision of the specific question has to be carried out in all applicable parts.

The authors of the PL must be made aware of the fact that similar 'patterns' might have to be corrected, not only single statements. The company must be open for quite substantial changes to the PL otherwise the testing will end up in trying to proof the quality of something which simply does not have the quality the test looks for.

Decision on further test rounds

It is worth contemplating the **success criteria** of Diagnostic Leaflet Testing, since reaching the pass mark or not has a major influence on the necessity of further test rounds and beyond that for further changes to the PL. Various pass marks exist that are described in the guidelines.[11,13,14,15,22] There is a whole range of options to interpret them. Fig. 3 in section 2.2.2 (*Pass marks of Diagnostic (Leaflet) Testing)* gives an overview of the main references and their interpretation. As many CROs for Diagnostic Leaflet Testing are UK based they are used to the UK pass marks for testing national UK PILs.

So, first of all the MAH together with the CRO has to decide which pass marks (section 2.2.2) are appropriate. Currently, there is no sense in applying the British 90 % / 90 % pass marks[14] on MRPs in cases where the UK is neither RMS nor CMS. Even with the UK 'on board', the 80 % pass mark can be regarded as the official one in Europe, as long as the Readability Guideline is under revision.

Final report

The final test report must fulfil two major requirements in order to avoid further changes to the PL during the assessment by the CAs. First of all, the report has to demonstrate that the overall test procedure was properly conducted and that the methodology is acceptable. The second objective is to demonstrate in the report that the underlying disease of 'all diagnosed symptoms' was cured effectively.

If the report fails to present the applied methodology in an appropriate way, there is the danger of non-acceptance of the test. This would result in a second test of the PL, which would probably have an impact on the PL. Currently, no European-wide assessment criteria are available that could serve as guidance for MAHs and CROs for the level of details required by CAs. Conclusions on requirement can only be drawn from national assessment criteria (if published) and retroactively by assessment reports (see also Appendix 3 *Assessment criteria from CAs).*

A conclusive discussion of the results obtained and the measures that were taken is very important to avoid any undesirable proposals from CAs on further 'improvements' of the PL. In this context it is of particular interest to tackle the comments and answers given by the interviewees to the general questions. Experience shows that the proactive approach of explaining attitudes towards sensitive issues is welcome at the CAs and often prevents further changes to the PL.

3.3 Impact on PL during MRP phase

The procedural steps for a MRP type II variation foresees a Preliminary Variation Assessment Report (PVAR) at Day 40 produced by the RMS. The PVAR is commented upon by the CMSs (until Day 55) and results in a request for supplementary information (RSI) to the applicant on Day 59. The RSI could be for a specific change to the PL.

The experience gained so far (Tab. 11) shows that there are relatively few comments on the content of the PL in terms of deleting, adding, or re-wording text in the PL. In addition, there are some requests on the design aspects (font size) of the PL, particularly since the new Draft Readability Guideline was published.

Tab. 11: Overview of requests from RMS and CMS during five regulatory procedures for PL harmonisation and PL-testing of MRP products. (Products A – E). Requests are grouped under deleting, adding, or re-wording text. Additionally, requests on format and design are listed, as well as the percentage of MSs that were interested in the discussion of the PL. The sections within the PL that were commented upon are indicated with the following abbreviations: I: Indications; W&P: Warnings and Precautions; IA: Interactions, P: Posology, ARs Adverse Reactions. ountries are indicated in brackets.

PL	Request to delete text	Request to add text	Request to re-word text	Request on Format and Design	MSs with comments
A[1]	I: Delete 57 % of proposed text (FR) P: Delete 7 % of proposed text (FR)	ARs: Clarify two terms by adding a few words according to the SPC (IE)		I: Move text FR wants to delete from section 1 to the end of MRP-PL, but maintain for national UK PIL (UK) General: Provide full size colour mock-up for decision on font size. (UK)	21 % (3 out of 14)
B[2]	IA: Delete 82 % of proposed text (FR)	W&P: Add cross-references to section IA / not recommended (FR)			33 % (1 out of 3)
C[1]	P: Delete dosage for special patient groups, delete overview table of various dosage regimens. (SE)		W&P: Change 'speak to' to 'please tell…' (DE) ARs: Combine two medical terms by one lay term (SE)		18 % (2 out of 11)
D[2]		IA: Add one INN as an example for a pharmacothera-peutic group. (SE)	I + W&P: Reword I and one W&P-statement according to SPC (SE)	ARs: Rearrange order of side effects so that side effects that require action appear first (UK) General: Enlarge font to 12 point for better readability (ES)	19 % (3 out of 16)
E[1]		P: Add standard sentence from QRD template (FR)			11 % (1 out of 9)

[1] Status: MRP phase closed. National phase ongoing.
[2] Status: PVAR and comments from CMS received.

Observations on these five examples lead to some preliminary conclusions about the impact of the MR phase on the PL. However, it is obvious that a few examples do not justify

conclusive statements. Only about 20 % of the MSs per procedure commented on the PLs at all. Although comments were scattered amongst sections and countries, the impression arises that several comments are purely driven by national attitudes from the past. This becomes evident when comments from Tab. 11 are compared with national attitudes from the past, as presented in Tab. 7 in section 3.1.2:

France: For product A FR requested a deletion of the major part (57 %) of the section on the indication. The text concerned was an explanation for the patient about the working mechanism and some basic information on the underlying disease that is being treated. For product B FR requested the deletion of over 80 % of the section on interactions. The whole section was targeted except for the interactions with medicinal product that are 'not recommended'. These requests come as no surprise. Tab. 7 designates FR as a **No-Explainer** for the indications, spending only 2.4 % of the total text on this section compared to 11.2 % that are deemed appropriate for the top 'Full explainer'. For the interactions attitude FR is part of the **Pointer** countries (Reference to the doctor) spending only 5.8 % of the total text compared to the maximum of 19.9 % for this section.

UK: For product A the UK responded with a creative, Solomon-like proposal to the French request to delete the major part of the section on indication. The UK explicitly stated that it welcomes the educational information in section 1 and wants to keep it in the national UK PIL. This attitude is in line with Tab. 7 that identifies the UK as a **Medium explainer** (Indication / working mechanism), spending 10.8 % of the total text on this section.

Sweden: For product B SE proposed the deletion of major parts of the section on Posology. This can be deduced from the national attitude of providing as little information as possible on this section and referring the patient to the physician even for the normal daily dose. Tab. 7 shows that SE as a **Non-performer** country places only 10.9 % of the total text on this section, compared to 24.3 % in case of the 'Full disclosure' performer.

Germany: DE made no comments calling for deleting text or simplifying expressions by also using lay terms. This is no surprise, since German texts are amongst the longest overall, adhering as closely as possible to the SPC text. However, a different national attitude is reflected in their meticulous comments, such as calling for the use of 'tell' instead of 'speak', or substituting 'if you are taking' for 'if you take'. It is the thoroughness and preciseness of 'The Germans' that lead to the eagerness to do these style exercises on an English text that is being translated anyway.

Returning to the question 'How big is the impact on PLs from the MR phase?' the answer is that the anticipated/proposed changes by single MSs may be profound. However, as substantial changes, triggered by specific national attitudes, are not enforceable at the European level, the PL at the 'end of procedure' of the MR phase is normally not changed in any substantial way.

In general, it is quite difficult for MAHs and CROs to anticipate the comments from CAs on harmonised PLs or the respective test reports. As mentioned in section 3.2.2, currently no European wide assessment criteria are (publicly) available. An EMEA press release[102] after a 'User testing and how to review the data' workshop declared that in a step-by-step approach the different views would be clarified. Until then the decision how the RMS assessed the harmonised PL and the respective report will be made case by case each time and when the MAH receives the PVAR he might get a surprise or two. Some country's comments will be more predictable than others, depending on the public availability of national assessment criteria (Appendix 3 for assessment criteria of CAs in UK, DE, FR, and NL).

3.4 Impact on PL during national phase

3.4.1 Translation

A *faithful translation* of the common agreed upon English PL version is the most crucial action after the end of the MR phase. Before national submission can take place, it has to be ensured that the nationally submitted texts are translations that still reflect the outcome of the 'user consultation'. This is clearly outlined in the *Guidance concerning consultations with target patient groups for the package leaflet,* which was issued in May 2006 and is now part of the Draft Readability Guideline. This document explicitly states that '*Strict literal translations from the original* [English] *language may lead to PLs which contain unnatural phrases …*' and this could consequently lead to difficulties for the patient to understand the text. Faithful translations allow for regional translation flexibility, whilst maintaining the same core meaning.

MAHs are asked to make every effort during the drafting of the 'original PL' to ensure clear and understandable translations. A negative impact on the PL during the national phase can be effectively minimised by the following actions:

- Ensuring that translators are native speakers (of the 'target language') and have a medical background. This will avoid translating for example 'Salmonella' as 'small salmons'.[99]
- Drafting of a translation guide such as an annotated version of the original PL with explanations of critical issues. This will avoid confusion about 'being sick' and 'feeling sick', or wondering about 'hives' what stands for 'urticaria' and has nothing to do with bees.
- Ensuring that translators also consider the corresponding SPC. This will avoid translations such as 'feeling sick'(nausea) as 'feel ill'.
- Performing a final check by a non-medical 'patient-level' native speaker. This may avoid terms such as 'flushing', which are primarily associated with 'flushing a toilet' rather than 'allergic flush'.

The aspect of initiating translations reasonably early to have enough time for review cycles was discussed in section 2.5 (*Company internal timelines for PL harmonisation process including PL-testing*).

3.4.2 Blue Box Concept – A loophole to deviate from a common agreed upon PL?

In contrast to the CP where PLs are commonly agreed upon for 10 years without the need for additional country specific text in national versions, the Blue Box Concept for decentralised procedures (MRP and DCP) allows for this specific information. This option results from the need to have at least some harmonisation between EU countries. In the NtA, Chapter 7, Section 10 the Blue Box requirements for Labelling and PLs in DCP or MRPs are listed. The following countries do not explicitly require additional information or text in PLs: BE, DE, EE, FI, FR, GR, LV, LT, MT, PL, PT, and UK. Two countries (CZ, IE) smartly state that such information for PLs could be specified in the future by the respective CAs (SUKL, IMB). Two countries (HU, SI) only require administrative information on the PL such as MA No. or legal status. Eight countries (Tab. 12) require additional content related information for PLs, even though these were in common agreement at the MRP level. Interestingly, SE, NO, and SK require the printing of this information in 'real' blue boxes on the PL.

[99] Example given by C. Wirthumer-Hoche during DGRA master studies in October 2004, Bonn

Tab. 12: Overview of countries that require Blue Box Concept information in the PLs that were commonly agreed upon during decentralised procedures. The sections concerned are indicated by the following abbreviations: I: Indications; W&P: Warnings and Precautions; IA: Interactions, P: Posology, ARs: Adverse Reactions.

Country	**Blue Box Concept requirements for PL**			
	Information about the possibility that 'real' indication and dosage may deviate from PL	Advice to contact doctor, hospital or poison centre (or pharmacy) in case of an overdose	Ability to drive and operate machinery / Warning triangle	Further Specialities
DK	W&P	W&P	W&P: Explanations	ARs: Encouragement to report side effects to Danish Medicines Agency
IS	I	P / Overdose	W&P: Statement	-
NO	I (in blue box)	I (in blue box)	W&P (in blue box).	-
SE	I (in blue box)	I (in blue box)	W&P (only if it is affected) (in blue box)	-
NL	I (for situations resulting from patent law)	-	-	P (for non-prescription only) / duration of treatment: Warning not to use medicine longer than 14 days (or other justified period) without consulting a doctor Section 6: MA number (RVG number)
AT	-	-	Pictogram	-
SK	-	-	-	Suggestion: Legal status including information about indications and dosage approved for OTC in a blue box
IT	-	-	-	ATC code 'Medicinale equivalente' (generics only) Statement on celiac patients (if appropriate) Statement for interaction with doping test (if appropriate)

The Blue Box Concept in general opens the way for additional country specific information on the PL, even when the main body of PL and SPC texts was commonly agreed upon (with no country specific modifications). There is an apprehension that this official leeway opens the door to compromise in seemingly hopeless situations and is seen as providing an easy solution or agreement between countries. For example in case of a debate of opposing positions during the MR phase one country might be persuaded to drop its request to insert a special warning or remark. However, during the national phase, this country will resurrect its original request, using the possibility of Blue Box Concept requirements. This loophole surely was not the initial intention of the CAs. However, it remains to be seen whether they will actually use it.

3.4.3 Timelines – approaching the vision of *within 30 days approval*?

As the main body of the PL text was agreed upon during the MR phase, the situation for national CAs in respect to workload during the subsequent national phase should have improved. Theoretically, CAs only check the Blue Box Concept information on PL and Labelling and also the faithful translation. Afterwards CAs should unblock the access of patients to PLs that are easy to comprehend, by giving approval for texts to MAHs.

However, the reality of three actual procedures shows that only in one procedure two (AT, PT) out of eleven MRP countries managed to release texts according to guideline[69] within 30 days. Even after 5 months there were no signs of feedback coming from the other CAs on harmonised PLs.

4 Conclusions and outlook

The last part of this thesis aims to draw general conclusions on the current situation from the various examples given throughout this study and it attempts to provide a scenario of what the future of PL-testing and PLs might be.

To start with, section 4.1 gives an overview of **how PLs change** due to the harmonisation process, the PL-testing, and the authority assessment. Additionally, some consideration concerning the role of **liability aspects** is provided. Section 4.2 probes the question of **how companies cope** with the demands of these new obligations. Later, in section 4.3, some thoughts are put forth on PL-testing, particularly the author's appraisal of the pro's and con's of **Diagnostic Leaflet Testing** which leads in turn to a consideration of the **future of PL-testing** as a whole (section 4.4). The final part (section 4.5) dwells on **future aspects of European PLs** from the content and design perspective and asks whether an approach might be developed to come to **patient tailored PLs** and the original aim of PLs that is supporting direct communication between patients and their physicians. Section 4.6 closes this chapter with final remarks on the overall context in which the PLs have to be seen.

4.1 How PLs change

As predicted earlier, from the perspective of established MRP products, the two prominent new requests for harmonised PLs and PL-testing in conjunction with authority assessment have a major impact on PLs that were written purely to conform with national legislation (even though based on the common *Directive 92/27/EEC*).

Harmonisation of PLs

The harmonisation process of PLs for established MRP products has the biggest impact on the content of European PLs as a whole. In particular the new QRD templates (November 2005), which were established for the decentralised procedures influence the volume of the various sections of a PL compared to the national approaches before NML. However, the degree of difference varies greatly between countries (section 3.1 *Creation of a harmonised PL*).

Central European countries such as AT, BE, DE, and NL are the countries for which the need for change tends towards providing less information overall. Their PLs might become less voluminous in the future since they should aim at concentrating on the information that is relevant to the patient and leave out information that is only useful for the physician. At present, in most sections of the PL these countries give a full disclosure of the information in the SPC.

Nordic countries such as FI, SE, and NO have to amend most of their sections by further explanations, including those on the effects of the interaction with other medicinal products. Also a full disclosure of information in the posology section will be standard in future.

UK/IE and DK are the countries where the biggest changes are expected, because up to now their approach has resembled a 'never-full-disclosure' writing style. In particular the deferral to the doctor that is made in the sections Interactions and Warnings & Precautions as well as the simplified Contraindications section surely do not fulfil pertinent QRD recommendations *not to omit complex details*[9] in here.

PT and ES are in most PL sections not too far away from current QRD recommendations. An exception is the section on Adverse Reactions that is not listed as a full disclosure of the SPC. Having the same situation in the UK/IE suggests that in PT and ES a similar attitude exists towards the interpretation of fulfilment of the *EC Product Liability Directive*. However, due

to the harmonisation of PLs it is to be expected that in these countries a full disclosure of Adverse Reactions should be forthcoming at least for decentralised products.

PL-testing / Diagnostic Leaflet Testing

In contrast to the topic mentioned above (harmonisation of PLs) the process of PL-testing does not necessarily lead to changes in the initial version of the PL. This is because it is up to the MAH to generate a high quality written and designed PL as an initial version to go into the PL-testing process. Depending on the effort and thought put into the creation process the PL will reflect this in the form of the amount of change that will prove to be necessary.

'As an ideal a PL should be so well written, clearly designed and printed, that any form of User-Testing would be demonstrably unnecessary.'

CROs tend to propose changes of the initial PL before entering the first interview round. However, in case it is difficult to follow the underlying reasons for these proposals, MAHs should critically discuss the motive behind those proposals with the CRO. Sometimes it appears to be difficult for CROs to admit that their customers might also be able to write usable PLs.

The main impact of PL-testing on PLs is an 'invisible' one. It consists of raising the MAH's awareness of writing a good PL before the actual test takes place. The MAH knows that choosing the right terms, expressions, and design may avoid the sword of Damocles coming down in the form of a test failure or a disapproval by the assessors. Therefore, *'As an ideal a PL should be so well written, clearly designed and printed, that any form of User-Testing would be demonstrably unnecessary.'*[100]

Authority assessment

Even if experience with authority assessment on PLs and PL-testing reports is limited to the few examples available for this thesis, the impression given is that there are overall only small changes of the **PL** due to the requests from assessors. Requests obtained so far were on the one hand editorial, such as adding (optional) standard phrases from the QRD template, or increasing the font size. On the other hand there were requests made to change the content of the PL, proposing text to be deleted, added, or re-worded (section 3.3, Tab. 11). Overall, these content related requests can be seen as indicators arising from the fact that national authorities have to accept a harmonised approach for PLs in accordance with QRD recommendations. An example of this is the AFSSAPS (FR) request to reduce information in section 1 (Indication) of PL to as little as possible whereas the MHRA (UK) opposed this position stating that they are very much in favour of educational information for the patient in this section.

Recalling the evaluation of PLs from various European countries in section 3.1.2 the characteristics of FR (29 words / 2.4 %)[101] and UK (121 words / 10.8 %)[101] in the indications section are perfectly in line with the requests stated above.

Overall, there is no tendency observable that assessors would get involved in detailed discussions about how to express complex medicational situations into patient understandable lay language. A possible explanation for this situation might be that assessors, often being under heavy time constraints, stick to their established approach to concentrate on the scientific considerations of the SPC and as long as its 'scientific content' is not visibly

[100] Radway-Bright E-L. ABPI User Testing Workshop, London; 20th September 2006

[101] Please refer to Tab, 6 in section 3.1.2 . %.- Figures indicate percentage spent on this section in relation to the whole PL text.

compromised in a substantial manner, they do not see any major need to evaluate the PL with the same time and effort. A further hint of the limited interest of CAs on PLs is the low attendance (around 20 %) at CMSs when commenting on the PVAR for the respective variation (section 3.3, Tab. 11).

So far, only few remarks concerning the **PL test report** were received. Assessors seem to have limited experience with this new piece of documentation, and may need further evaluation guidance (EMEA press release).[102]

Some authorities quite openly display what their criteria for assessment are. Examples from BfArM (DE), MEB (NL), and MHRA (UK) are shown in Appendix 3. The MRFG/CMD(h) announced in the concept paper on achieving harmonised patient information[86] a '***new standard operating procedure on assessment*** *and the associated MR/DC timetable'* being *'under development'*.

Knowledge about assessment criteria or the assessment procedure is very welcome at pharmaceutical companies and CROs, so they could take into account any specific requirements which the CAs have. For example the MHRA needs a full size full colour mock-up of the PL to evaluate layout and content, whereas the BfArM has its main focus on assessing the PL-testing report.

Liability

The regulation of liability claims did not change due to NML. The core foundation of pharmaceutical law is classified as administrative law (e.g. obtaining a MA) being influenced by civil law (e.g. liability law) and criminal law. Some countries combine aspects of all three forms of law in their national law on medicinal products, e.g. in DE liability law is covered in §84 of AMG.

Particularly the strict liability system contributes to the huge amount of information often covered by a PL. Under strict liability law companies are not protected if a new risk emerges which is not covered by a warning. However, despite imposing the system on the whole EC via *Council directive on the approximation on the laws, regulations and administrative provisions of the Member States concerning liability for defective products (Directive 85/374/EEC)*, there are quite different interpretations of how this legal obligation may be met. In DE this system existed particularly for medicinal products several years before the 'Product Liability Directive' came into force.

The German AMG §84 (1) states that the MAH is liable in case the reason for damage lies within the SPC, PL or Labelling that are not drawn according to current scientific knowledge of the medicinal product. Obviously, it was interpreted in a way that most information of the SPC had to be in the PL as well, irrespective of its usability for the patient. Matters worsened when the 12th amendment of the AMG came into force on 6 August 2004 stipulating that the PL is the basic document of what to judge if an undesirable effect is expected or not (§4 (13)). This leads to the need to have in the PL every single adverse reaction mentioned in the SPC.

A totally different approach to fulfil the 'Product liability directive' (*Directive 85/374/EEC)* was taken by the UK. At an international symposium (1988) a representative of the ABPI said that his organisation believed that it had met UK and EEC liability requirements by stating in PPIs (PLs) that further information was available from doctors and pharmacists.[103] His view was shared by UK lawyers at the Department of Health.

[102] EMEA/457658/2006: Press release: The EMEA and the CMD(h) review Europe-wide experience with user consultation in the readability testing of package leaflets; 15 November 2006

[103] White S. SCRIP No 1350: Patient information in Europe; 7 October 1988

A question very often raised is: *Are the legal requirements to PLs patient-oriented?* [104] Considering the requirements on PLs due to legally binding acts (as defined in NtA 2A, Chapter 1), particularly *2001/83/EC as amended Art 59* and in general *85/374/EEC*, the reproach is that '*instead of an patient oriented Information the result is an unreadable, incomprehensible 'blurb''*.[104] Investigation of the correlation between length of text, comprehensibility and compliance led to the conclusion that the crucial point is to shorten the patient information in order to enhance the contribution of PL to the safe and effective use if medicinal products:[104,105] *Increased comprehensibility is only achievable by slimming the catalogues of 'required' information.*[104] However, it was left open if that should be achieved by change of the law or through appropriate interpretation of how to fulfil the legal requirements.

Countries such as the UK have shown that short and relatively simple PLs are possible, if deferral to the physician or pharmacist is made instead of providing full disclosure of complex information on interaction, side effects, or dosage as a way to meet the obligation under the law. This approach is of course subject to the interpretation of CAs and courts.

However, answering the question raised above with respect to 'Soft law' (as defined in NtA 2A, Chapter 1) would probably lead to a '*slimming of catalogues'* answer. Particularly the QRD templates, now also applicable for decentralised procedures and many national procedures, narrow the latitude for interpretation and product specific design. Surveys amongst patients[106] indicate that patients have different preferences. Another criticism is that at the same time, when PL-testing was made mandatory, the newly defined structure and content for PLs, i.e. the QRD templates, did not reflect testing in order to fit into the whole concept.

In addition, in the case of compiling harmonised PLs the principle of '*the lowest common denominator is the sum of all single countries*' applies. This leads to a PL that covers in each section the requirements of the country with the most extensive information requirements.

Neglecting the legal requirements and instead concentrating on the needs indicated by interviewed patients leads to experiments such as the WIdO Study[106] in Germany. In a cooperative study, the association of customer advice centres (VZBV) and a health insurance organisation (AOK) asked future customers of PLs about their needs and their prioritisation of information about medicinal products. As a result a PL was developed that impresses on by its brevity, layout, simple language, and good graphic features. As legal requirements were completely ignored during creating this PL, there is little probability that any CA will accept it. However, instead of searching for an approach like 'Making the best out of it', i.e. fulfilling the legal requirements and compensating for their drawbacks with enormous efforts to provide an optimal interpretation, the conclusion out of the WidO study was that ' …*in case of doubt the legal requirements have to be changed – not the customer!'*

' …*in case of doubt the legal requirements have to be changed – not the customer!'*

[104] Meyer J. Pharm Ind 52, Nr 10. Arzneimittelsicherheit durch Gebrauchsinformation – Sind die rechtlichen Anforderungen an die Packungsbeilage patientenorientiert?; 1990

[105] Ley P, Jain VK, Skilbeck CE. Psychol Med 6:500-601. A method for decreasing patient's medication errors; 1975

[106] Nink K, Schröder H. WIdO-Materialien Bd. 53, 138 Seiten, Bonn. ISBN 3-922093-39-6. Zu Risiken und Nebenwirkungen: Lesen Sie die Packungsbeilage?; 2005

4.2 How do companies cope

Pharmaceutical companies doing research in **ethicals** have to adapt their development plan in the 'final phase before submission' part. However, comparing the cost and resources for PL-testing (section 2.4. *Budget / resources*) with the overall average expenditure of about 895 million € per NCE,[107] does not make the new requirements a new, major hurdle. On the other hand, the retroactive applicability of PL harmonisation and PL-testing leads to a case-by-case re-evaluation of the cost effectiveness of the products that are already on the market.

Pharmaceutical companies in the **generics** sector struggle a lot more with this process. Often their product portfolio is very broad, therefore a much larger number of PL tests is needed. Because the profit margin is lower in the generics business, the case-by-case re-evaluation of the cost effectiveness of the products that are already on the market might more often be to the disadvantage of maintaining the MA. However, generic companies have started building alliances, such as a library for PL tests, where each contributing generics-company is allowed to use the PL tests of the other participants.[108] Such an approach by the British Generic Manufacturing Association (BGMA) is supported by MHRA and the initiative is taken forward in Europe via the European Generic Medicines Association (EGA).

When trying to give an answer to the question 'how do companies cope?' there is another point of view which must be mentioned as there are two sets of companies to be considered. On the one hand there are pharmaceutical companies that struggle with the new requirements to provide results to the CAs and on the other hand there are companies that make it their mission in life (as a company) acting as **CROs** to generate the data 'Big Buck Pharma' needs. There are even new companies founded solely to perform PL-testing. These companies have evolved throughout Europe, but the highest proportion is located in the UK. This is due to the fact that in European procedures the report on PL-testing with all its Appendices has to be delivered in English and most companies focus on the Diagnostic Leaflet Testing method, where native speakers are needed as interviewees. In addition, many CAs accept PL test reports on PLs in any of the European languages (including English) for their national MAs.

4.3 Strengths and weaknesses of Diagnostic Leaflet Testing

Transcendent view of Diagnostic Leaflet Testing

The initial intention of the diagnostic testing approach for PLs is to ensure that the PL can be actually **used** by people. This means that people can act appropriately in various situations that call for different responses and actions. However, this test is only valuable from the regulatory point of view, when the symptoms 'diagnosed' on the PL can be cured in a way that is accepted by the CAs. In Europe a purely 'content based regulation' was valid until 30 October 2006. The term content based means that regulations instructed the designers of PLs what information must or must not be included in the PL and as a rule even the order of sections was specified.

These constraints may reduce the benefits derived from the Diagnostic Leaflet Testing, which are only fully effective in a 'performance based' regulation field. 'Performance based' means that regulations specify the performance that people should be able to do, e.g. with a leaflet. This performance enabling requirement was explicitly and newly introduced by *Directive 2004/27/EC Art 1. 48) b.*: '*The package leaflet must be written and designed to be clear and*

[107] http://www.efpia.org/tools/faq.htm#Ancre5 (accessed 4. 2. 2007)
[108] SCRIP World Pharmaceutical News; UK generics firms set up bank of user-tested patient leaflets. 15 February 2007

understandable, enabling users to act appropriately, when necessary with the help of health professionals.' However, the 'old' content based requirements were not changed or adapted to provide the option to implement the new performance based regulation.

The diagnostic testing itself might be a powerful instrument that could lead to 'usable' PLs. However, as long as the general requirement for PL-testing is not embedded in a performance based regulation and is not free from interference of content based regulations, the development of usable PLs by diagnostic testing can not take place to the full benefit of patients.

Simple examples of this problem are the mandatory statements in the QRD templates such as Appendix III statements for storage (e.g. *Do not store above 25°C.)*. The current approach to avoide trouble that would result from people 'not understanding' when asked about storage conditions, is simply **not** to ask these kind of questions altogether.

> *'It reads: 'Do not store above 25°C.' Does that mean I can put it in the freezer?'*

Imminent view of Diagnostic Leaflet Testing

The advantages of Diagnostic Leaflet Testing can be summarised as follows:

- High acceptance at European CAs
- No need for a validation/verification44 data package
- Easy to be performed, detailed description available
- Easy access, as many CROs offer Diagnostic Leaflet Testing as service

The limits and disadvantages of Diagnostic Leaflet Testing are:

- Neither the validity of the method ('do questions about a text really measure its readability?') nor the score ('is 16 out of 20 really acceptable?') have been investigated.[109]
- The bias that is exerted by the interviewers via 'body language' on the interviewees and their responses might be significant. In addition the interpretation of answers given verbally to open questions may leave too much room to the interviewer to 'bend' in favour of the PL.
- No (statistical) justification is available for a limitation to 20 participants.
- Interviewees are in a stress situation, although they are reminded that it is the PL which is the tested subject, not the interviewees.

Taken together there are a lot of pitfalls when conducting Diagnostic Leaflet Testing with a honest intention. However, due to the lack of better well known and widely accepted alternatives, Diagnostic Leaflet Testing will probably remain in the near future the leading PL-testing method.

4.4 Future of PL-testing methods

Currently it seems very likely that the only way to get to alternative PL-testing methods others than the well-known Diagnostic Leaflet Test is via their 'official' and 'public' acknowledgement by the European CAs. The example of the Diagnostic Leaflet Testing method shows that most pharmaceutical companies 'jump' on this method in order to save as

[109] Dr Karel van der Waarde, Graphic-Design Research; May 2005

much time and money as possible. This is the outcome of a situation where a proposed test method is described in detail in a guideline, with no need for further verification/validation data to be submitted by the applicant.

It may well be significant that the development of the Australian Diagnostic Leaflet Testing method was not performed by a 'private' company in Australia. It was initiated by the TGA in collaboration with the CRI, and financed by the Australian government. Probably this collaborative approach may well be the best way forward for establishing further, alternative test methods.

Surely, the way is open for other companies or CROs to establish their own testing methods, but the onus is on them to convince the CAs that the new method is as effective as the gold standard of PL-testing methods, i.e. the Diagnostic Leaflet Testing. Convincing CAs is done by providing data for verification/validation of this new method. As with all generated data packages there is an issue with intellectual property rights, which are in the possession of the company or group that created the data. Companies seeking CROs for performing PL tests can buy a combined package of test performance of the specific PL together with the underlying data for method verification/validation.

Such an approach was successfully done by PAINT-Consult, a German company founded by Jörg Fuchs performing the '**Written readability test'** (Appendix 2 for details). This test approach is also explicitly mentioned on the German CA's (BfArM) homepage as being one of the test methods acknowledged by BfArM.[110]

A further successful approach, the Austrian *Psychological Analysis of Patient Information* (**P.A.P.I.**) performed by 'Das Psychotechnische Institut' in Austria[53] (Appendix 2) was also well received at the respective Austrian CA (AGES). Their approach to PL-testing (section 2.1.4 / P.A.P.I.) is strongly supported by representatives of the Austrian CA. Their goal is to have this test method as a further example of how a PL test can be performed in the future Readability Guideline. This would mean it is 'free of charge' just like the Diagnostic Leaflet Testing method. However, as performance of P.A.P.I. is quite complex and needs specific skills, pharmaceutical companies would still have to rely on the charged services of appropriate institutes or CROs. P.A.P.I. aims to not only test the legibility and comprehensibility of the PL by potential patients, but also investigates the emotions which the PL triggers in potential patients.

There are two major aspects why this information is useful to have for the MAH in addition to the 'quantitative' test results:

- **Compliance aspect**: One of the prerequisites for a successful treatment is the compliance of the patient. Compliance is increased if the patient is convinced that the medicinal product will have (overall) positive effects. P.A.P.I. examines whether the PL or some specific parts of it trigger fears in the readers and 'put them off', leading to diminished compliance.
- **Marketing aspect**: When a patient acknowledges a PL (overall) as positive, one of the marketing goals is achieved. This implies a positive image of the medicinal product and therefore of the MAH. All this triggers marketing effects such as word-of-mouth influence or asking for a medicinal product from the same MAH when the next (different) sickness occurs.

[110] http://www.bfarm.de/cln_043/nn_424304/SharedDocs/FAQ/DE/Arzneimittel/pal/fa-ampal-faq.html (accessed 12.1.2007)

Currently, the disadvantage of this method is its limited publicity at European CAs other than the German speaking ones. In addition, it is limited due to the fact that currently only the Austrian 'Das Psychotechnische Institut' is fully competent in performing the P.A.P.I.. However, according to guidelines it is possible to have the PL tested in any European language. Therefore, it should be possible to submit the Austrian P.A.P.I. test report after translation into English to European CAs, at least for use in European procedures (CP, DCP, MRP). The second point about limited accessibility might be solved in the future, since the Austrian 'Das Psychotechnische Institut' plans to approach other marketing institutes in various European countries to provide them with necessary information and enable them to perform the P.A.P.I..[111] As institutes in other European countries would also use their respective languages, the 'language problem' would be solved as soon as the first institute in the UK or IE offers this service.

A different approach to evaluate PLs for patient usability is presented in the following although it has not generated a usable method up to now. However, it does show exemplarily the general approach towards developing new methods:

Gustafsson et al.[112] described how experts and patients evaluated patient information leaflets from 30 common medicines by means of standardised questionnaires. '*The hypothesis was that if there was a correlation between the results of these evaluations it would be acceptable to only do the expert review for patient information leaflets currently in use*.'

The trigger and background for that study was the EMEA recommendation for user testing in 2000 that lead to the conclusion that '*such tests would require the involvement of patients and would therefore be complicated to conduct and difficult to standardize. Furthermore, tests of all patient information leaflets in circulation in a country at any given time would be a very large endeavour.'*

The outcome of their study showed that there was a significant correlation between the scores of the experts versus those of the patients in the examination of the content. However, the scores regarding language and layout did not correlate at all, and therefore the overall scores for the leaflet did not correlate significantly. Nevertheless, Gustafsson *et al*. concluded ' *that the test of patient information leaflets could be limited to expert testing of language, layout, and content*.' They further specified '*that a leaflet of good quality should score above the average in both the language/layout test (>16 points* [out of 25]) *and the content test (>21 points* [out of 25]). *Such a leaflet is also likely to score high in the patient content test.'*

Overall, this study is an interesting approach of how to reduce the need for resources and man power while fulfilling the requirements. However, digging a little bit deeper into the publication reveals certain weaknesses. The most important one is that content related questions of the standardised questionnaires are not suitable to reveal correlation in the experts' and patients' evaluation of the leaflet: Where the content related questions for the experts are a mere 'check list test' about consistency with *Directive 92/27/EEC*, the respective questions for the patients aim at comprehensibility testing of the information contained in the PL. These are not really the sets of data which should be correlated. This is rather like comparing apples and oranges.

From today's perspective with the Diagnostic Leaflet Testing being considered as the 'Gold standard' for PL-testing, the above described verification approach is deemed as insufficient, as the data comparing the proposed method with the standard method are missing. However,

[111] Dr. Susanne Hackl-Grümm, Psychotechnisches Institut, Austria, Personal Communication.
[112] Gustafsson J, Kälvemark S, Nilsson G, Nilsson J L G. Drug Inf. J 37:115-125. A method to evaluate patient information leaflets; 2003

there are many theoretical ideas for alternatives to the Diagnostic Leaflet Testing and it remains to be seen if companies, institutes, or other interested parties will successfully demonstrate their equality to the gold standard. This is preferably done in cooperation with CAs to ensure the acceptance and to obtain better publicity.

Implications for future requirements worldwide

By implementation of *Directive 2004/27/EC* Europe is the first multinational and multilingual region worldwide with a legal requirement of conducting PL-testing and providing results to the respective CA. In quite a few countries outside the ICH region requirements for obtaining MAs for medicinal products are modelled on the requirements in Europe. It will be very interesting to see if, when, and how countries outside of Europe will transfer the need for PL-testing into their own laws and guidelines. It will be particularly exciting to see if these countries make the Annex of the MHRA guideline mandatory, together with the need to test in the local language. Maybe (pharmaceutical) companies should start to think of how to conduct Diagnostic Leaflet Testing in Swahili, Russian, Urdu, Arabic, or Afrikaans etc.

Specifically countries that already require their PLs in the format of the Model Leaflet (Annex 1a to Readability Guideline of 1998), such as ZA, should be closely observed for changes or adaptation in their requirements.

In addition, it will be interesting to observe the European ICH partners Japan and the U.S.. Even when Module 1 is not part of the 'classic' CTD and the requirements contained therein can not be transferred, there exists the claim by the WHO that 'patients have the right to be given factual, supportable, understandable and appropriate information, to be provided in such a way as to allow them to decide whether they wish to receive therapy' (World Health Assembly Declaration 1994).[113] This might lead indirectly to changes in the aforementioned countries as well.

4.5 Future of European PLs

Content aspects

European PLs are expected to achieve a similar level of quality through the common standard determined by QRD templates and the new revision of the Readability Guideline. Some countries may have to move down to that standard, but most will have to raise their current levels in terms of the volume of information given. The different interpretations of current law in different EU-countries becomes particularly obvious during the harmonisation of PLs in established MRP products (section 3.1.2).

The difficulties with the balancing act between the strict liability system and the duty to inform the patient properly were addressed much earlier than the adoption of *Directive 2004/27/EC:*

> *'The pharmaceutical industry is particularly concerned at one aspect of the inter-relation between product labelling requirements, product safety and product liability. Directive 92/27/EEC specifies the requirements for the labelling of medicinal products and package leaflets. Details must conform to the summary of product characteristics. In providing information to patients,* ***it can be difficult to strike a balance between****, on the one hand,* ***simple and comprehensible information*** *which will encourage safe use of medicines and,*

[113] Collier J. The Lancet 352:1724. Commentary Patient-information and prescriber competence; 1998

> *on the other hand, information which is **sufficiently detailed** so that the producer clearly has no liability because lawyers might criticise it on the basis of lack of information.'*[114]

The general comments of EFPIA on the Draft Readability Guideline of 2006 visualises the uncertainty at companies:

> '*We note that there is no guidance at all as to which and how much information the package leaflet shall contain. From the QRD templates, some information can be drawn. However, it remains unclear whether all side effects must be listed, or dosage recommendations for special patient groups must be given, or patient groups not studied should be mentioned in the leaflet, etc…'*[115]

It remains to be seen if CAs will take this advice and make such detailed recommendations at the European level. This is unlikely, as this would strongly interfere with the complex situation of liability issues. It is the MAH of the medicinal product who is liable in case of failure. Therefore no CA would succeed in suggesting a listing of only the serious side effects and omitting others, as long as national interpretation of liability requirements would lead to major disadvantages for the MAH in doing so.

On the other hand there are already national CAs that give detailed guidance in their national interpretation of the QRD templates. An example is the MEB (NL), which explicetly explicitly asks to have in the PL **all contraindications** stated in the SPC as well as in principle **all side effects** that are included in the SPC, followed by extensive explanations.[83]

Overall, the European PLs will probably lengthen. On the other hand, due to requirements for PL-testing, this might be compensated for by a well designed and well structured lay out and the use of patient friendly language.

Last but not least: It is likely that speculations will start on what might be the effect on PLs or their tests after the first court case has ruled in favour of a plaintiff who claims a medicinal product to be defective because the PL is not to 100 % understandable. The MAHs have to keep in mind that at the same time they prove that 80 % or 90 % of questions or people succeed in a PL test, they also prove in the same instance that 20 % or 10 % do **not**.

Design-aspects: Navigation aids / Pictograms / Symbols

Taking for granted that there is not much hope of a dramatic reduction of the sheer amount of text that has to appear on a PL, due to regulatory, QRD, or liability reasons, an option to nevertheless improve the easy access for the patient is to sharpen up the **navigability** of the PL. Having six major heading and several sub-headings implemented via QRD templates is fine, but it is still 'only' text. Pictograms or symbols capture the attention of the 'reader' via different perception means, and these alternative tools are generally positively perceived.

Although pictograms and symbols are generally allowed for use in PLs (*Directive 2001/83/EC as amended, Art 62*) their actual use is currently limited to the Blue Box Concept. There is no 'voluntary' use in the commonly agreed upon main body of text of the harmonised PLs resulting from decentralised procedures. Symbols and pictograms offer the opportunity to make PLs easier to cope with e.g. by letting the reader navigate them with greater ease through headings and accompanying specific symbols. This leads eventually to more reader friendly PLs. However, this option is generally not used, probably as there is currently no common set of symbols and pictograms agreed upon (and tested) throughout Europe. Although, this would be a prerequisite for MAHs before using them for MRP-PLs on a voluntary basis. Currently MAHs have to explicitly demonstrate that there is no doubt about

[114] EFPIA: Position paper Green paper on liability for defective products, Section 10.5; 1999
[115] EFPIA comments on Draft Readability Guideline of September 2006

the meaning of a specific pictogram, particularly when transferred or used in other language versions of the PL. This demonstration would have to come in the form of further PL-testing (Draft Readability Guideline 2006).

Throughout the world, there are only few examples when the use of pictograms became standardised on an international level. The best example resulted from the cooperation between the American Institute of Graphic Arts (AIGA)[116] and the US Department on Transportation. They developed a set of pictograms that influenced the use of pictograms worldwide in the area of transportation (train, airway, water transportation).

Fig. 10 Symbol signs developed by AIGA in the area of transportation. Symbol signs stand for (from left to right): Telephone, mail, nursery, information, toilets-men, toilets-women, first aid.

We can take the example further with the All Japan Airport Terminals Association, Inc. (AJATA) [117] which developed a set of pictograms which were nearly identical to the AIGA symbols. They made only slight amendments and developed some additional symbols for issues not yet covered. This US-based Japanese approach demonstrates the high intercultural acceptance of symbols.

Big international sport events such as the Olympic Games 1972[118] in Munich, Germany, the Olympic Games 1988[119] in South Korea, or the Soccer World Championship 2002[120] in Japan/South Korea, also triggered the creation of internationally comprehensible pictograms. Interestingly, transportation pictograms all strongly resembled the AIGA pictograms or were even identical. In addition pictograms reflecting the various sport disciplines were developed for these events.

The answer to the future needs of the European health sector, may well be the establishment of a 'European Pictogram Task force for Medicines' (EPiTaM) composed of regulators from European CAs, marketing analysts, and people familiar with the process of developing those symbols for sport events and transportation mentioned above. Such a task force should be able to develop a set of pictograms applicable to the use in PLs to assure easy navigation and to highlight important sections. If developed in the same manner as the worldwide known pictograms for transportation and sport events mentioned above, as well as considering the ISO guidelines 7001:1990[121] and 9186:2001[122], a high level of acceptance by consumers, MAHs and authorities is very likely, and worldwide acceptance might come eventually. A further valuable partner on the way to European wide regulated pictograms might be the various national organisations in the field of norms. For example in Germany the Deutsches Institut für Normung e.V. (DIN) could be approached to participate in the EpiTaM, maybe after having been the lead in a National Pictogram Task force for Medicines (NaPiTaM).

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[116] http://www.aiga.org/content.cfm?ContentID=147 (accessed 18.1.2007)
[117] http://www.get2testing.com/Pics_AJATA.htm (accessed 15.1.2007)
[118] http://www.get2testing.com/Pics_ERCO.htm (accessed 15.1.2007)
[119] http://www.get2testing.com/Pics_O_88.htm (accessed 15.1.2007)
[120] http://www.get2testing.com/Pics_ECOMO.htm (accessed 15.1.2007)
[121] ISO 7001:1990 defines a set of pictograms and symbols for public information. The set is the result of extensive testing in several countries and different cultures and has met the criteria for comprehensibility set up by the ISO. Common examples of public information symbols include those representing toilets, car parking, and information.
122 ISO 9186:2001 proposes a procedure for testing graphical symbols that allow for two tests, a comprehensibility judgement test and a comprehension test.

Is there a future for patient tailored PLs?

Improving navigability of lengthy PLs via symbols, pictograms, or bold text could be developed further via the generation of patient tailored PLs. Assuming that in the near future there is no 'legal' way to shorten PLs dramatically or replace whole sections by a reference to a physician, pharmacist, web page, or European Public Assessment Report (EPAR), an answer to this problem could be to guide the patient via the generation of 'personalised' and situation tailored PLs.

The main idea would be to switch from standard PLs printed and packed by the MAH towards computer generated PLs printed in pharmacies. At least for prescription-only medicines, which tend to have the longer and more difficult PLs, the process might be imagined as follows:

- During patient consultation at the physician the patient's health insurance chip card is connected to the computer when the physician intends to prescribe a medicinal product. After the name of the medicinal product has been entered, the respective PL pops up on the screen.
- A software program generates a draft patient tailored PL version by comparing the patient's health data (age / sex / current medication / concomitant diseases) with the information on the PL. All information applying to the specific patient's data would be 'highlighted' e.g. displayed with a yellow background instead of a white one. The result would be that in the interactions section (for example) only information on currently taken co-medication is highlighted; whereas the whole contraindications section would not be highlighted, as their absence should have been ensured by the physician beforehand.. In the dosage section only the recommendations for the appropriate age group is highlighted; and in the Warnings & Precautions section only the information that is relevant because of concomitant diseases, as well as general information.
- The physician and the patient review the displayed version by asking relevant questions such as: Do you currently take any other medicines that are available without prescription? The physician appropriately amends the proposed PL version by clicking on the respective interaction information, if any is available (Clicking on a text module will lead to highlighting).
- The physician then stores the patient tailored PL version together with the prescription in electronic form on the patient's health insurance chip card.
- The patient goes to the pharmacy, where the pharmacist inserts the patient's chip card into the computer to access the prescription and to print the computer generated patient tailored PL. The PL is personalised for the patient by printing the name of the patient on the heading: Package Leaflet: Information for Mr. Joe Public, and by stating in the introductory sentence of the PL the phone numbers of the prescribing physician and the pharmacy where the PL was printed. In case the patient is vision impaired a larger font for printing could be chosen, such as 14 point.
- The pharmacist takes the leaflet out of the printer and gives it to the patient together with the medicinal product. This is the optimal opportunity for a quick review with the patient of the entire leaflet, to ensure that the leaflet is 'readable' in technical terms and to point out the meaning of the highlighted sections in particular.

Several conditions would have to be met to make this vision of information supply to the patient operational:

- Political permission to 'go ahead' with storing 'health history' on health insurance chip cards
- Coding of PLs, database for coded PLs

- Development of a software, that combines information from health insurance chip cards and coded PLs to generate the proposed patient tailored PLs
- Common online database (at least per EU country) for all authorised PLs in the appropriate electronic format.
- Computers and printers at all pharmacies, computers at all medical practices

The FDA Stuctured Product Labeling (SPL)[123,124,125] approach has evolved in parallel to the PIM approach[85] in Europe. Even if they have different primary use cases, they are both XML based and there already exist software tools that can handle both formats.

In the U.S. SPL captures the text of the prescribing information (including the 'Highlights' section and table of contents, in case of 'new format labelling') and any FDA's approved patient information (medication guide or other). In case of an existing 'Highlights' section, much of the clinical content of those 'Highlights' is also 'coded' for the use in clinical decision support systems. This is achieved via a computer-assisted comparison between the patient's electronic health record and the SPL coded parts of the U.S. PI. For this purpose a common database (DailyMed[126]) was set up that facilitates access to the PIs for the 'clinical decision support systems'. It might be worth to consider the application of this SPL assisted technique to the European PLs in order to realise the vision described above.

Even when some of these prerequisites seem far away from European reality, it should be pointed out that there are countries which manage computer generated leaflets, coding of medicinal product information, and storing of health history on chip cards. Even in Europe are countries that have had bits and parts of the vision outlined above. According to Stichele and Bogaert[18] in the Dutch PHARM-ROM system a CD-ROM player is available in community pharmacies to produce patient leaflets, tailored to an individual patient in an individual situation. In Finland there is at least a system established to print out summaries of PLs at community pharmacies.[19] These summaries are written by the Medical information centre, but not patient tailored.

A further requirement is that there needs to be the regulatory framework and culture to support such an approach. For example *'The **inclusion in** the packaging of all medicinal products of a package leaflet shall be obligatory unless …'* (*Directive 2001/83 as amended Art 58*) has either to be adapted or must be interpreted in the sense of: '*Every medicinal product must be **accompanied** by a PL unless …'*. However, this would invite or cause various changes that are not easy to foresee, for example the procedures for final release may have to be organised in a different way.

In the regulatory field of pharmaceuticals there is always room for improvement. Staffs coping with regulations at both companies and CAs are in a constant struggle for better medicines. It is possible that patient tailored European PLs are developed and become a reality in the near future, if concerned parties are able to build on what has been achieved up to now, consider new approaches and opportunities of single parties or different countries, and are, last but not least, willing to 'think outside the box'.

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[123] FDA. Guidance for Industry: Providing regulatory submissions in electronic format – Content of Labeling; April 2005

[124] FDA. SPL Implementation Guide for FDA Content of Labeling Submissions Version 2a/Rev.1, October 2005

[125] An SPL document consists of an XML file that contains the content of labeling (all text, tables and figures) for a product along with additional information for machine processing of label content (header information and data elements). The SPL XML file may be displayed (rendered) in a human-readable format by the use of a set of files collectively referred to as style sheet. Using a web browser, the style sheet displays the information in the XML file in a consistent format for viewing.

[126] DailyMed, is a new way to distribute up-to-date and comprehensive medication information in a computerised format for use in health care information systems. http://dailymed.nlm.nih.gov/dailymed/about.cfm (accessed 1.2.2007)

4.6 Final remarks

European PLs are important documents that accompany medicinal products and provide information that is exclusively addressed to the patient. In the respective European countries PLs were introduced in different years and developed at different rates of speed. In some countries the first mandatory PLs were addressed to the physicians, while other countries did not have any mandatory PLs until they joined the EU and had to accept and implement the *acquis communitaire*.[127]
Different health systems, as well as different national attitudes towards health care, physicians, and medicinal products in general led to quite different interpretations of how to fulfil the requirements of *Directive 92/27/EEC*, the first European Directive regulating the content of European PLs.

Before *Directive 2004/27/EC* all PLs had to fulfil two major tasks. The first task was to provide 'full disclosure' information to the patient, so that the patient himself could theoretically do a risk-benefit-analysis of taking the medicinal product by himself. As a result the patient would act on the basis of a 'pharmaceutical informed consent'.[1] The second task was to protect the MAH against law suits. The 'strict liability system' applies in all European countries since the 'Product Liability Directive' (*Directive 85/374/EEC*) came into effect.

With *Directive 2004/27/EC* in force there is at least one additional task that the PL has to fulfil: It must be written in such a way that patients can act appropriately on it. This feature has to be demonstrated via a report on successful PL-testing that is to be submitted to and assessed by CAs.

Besides all these 'hard facts' there are also 'soft facts' that are absolutely necessary to be considered in the circumstances surrounding PLs:

- **PLs are not always read**
  Despite all efforts to style patient friendly PLs and prove their usability, this does not necessarily change the attitude of certain patients towards *starting* to read a PL. Whether a patient reads a PL or not, does not dependt solely on the PL's lay out or writing style. There are so called 'patient factors'[37] that have a great impact on overcoming the first hurdle towards reading a PL, which is having the intention to do so, searching for the PL, unfolding it and starting to read it.
  The coping style is one of these patient factors.37 Coping is the mental behaviour of how to deal with his/her stresses and choose a procedure based on his or her perception of the problem (illness). There are two major coping styles that can be observed. While certain patients cope by becoming actively involved in their treatment and seeking as much information as they can, other patients cope by avoidance and behave passively towards obtaining information. This latter group of patients would not seek out and go through a PL on a voluntary basis.

- **PLs are only one half of the complete picture**
  The first choice for patients on how to obtain information on medicinal products is to receive it from the physician or pharmacist by verbal explanation. It is the duty of the physician to explain the pro's and con's of a medicinal product in the specific patient's situation. He has to explain to the patient in an appropriate style the basic facts needed for an informed decision. The consumer has the right to know, to make informed choices, and to participate in the healthcare system. It is important that PLs are used as a

[127] This term is used in the European Union law to refer to the total body of EU law accumulated so far.

tool for improving the physician patient communication rather than being a replacement for it. In such a setting PLs serve as an *'aide memoire'* for the time when the patient is back at home and wants to recall some information. In addition the PL is the basis for the 'pharmaceutical informed consent'1 However, as 'real life' shows, the patient is very often left on his own with a prescription and the associated medicinal product accompanied by a PL, which is the only source of information.

- **PLs are not the only written source of information for patients**
  PLs have to be seen as an integral part of educational strategies, which are designed to promote health. With the wide distribution of the internet and its huge amount of information patients have access to a vast number of health related websites. Much of the health related material on the internet is misleading or inaccurate. It is particularly difficult for the patients to sort out the wheat from the chaff. In analogy to the *Evidence-based medicine*[128] approach first attempts towards *Evidence based patient information* are being undertaken or at least considered.[129] It is crucial that PLs as a central document set a good example in providing scientifically accurate facts that are easily digestible by laypersons.

[128] *Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.* (www.acc.org/qualityandscience/quality/evidence.htm, accessed 19.2.2007)
[129] Coulter A. BMJ 317:225-226. Evidence-based patient information; 1998

5 Summary

The present thesis describes the impact of two new European obligations on the business processes of pharmaceutical companies as well as on package leaflets (PLs).

Package leaflets in Europe have several roles to fulfil:

- They are part of the Marketing Authorisation (MA) for medicinal products, as well as of the 'finished package' for distribution. According to *Directive 2001/83/EC* as amended Art 59 they are in general an obligatory part of the medicinal product, with detailed requirements on their content, and are directed to the user, in most cases the patient.
- The information PLs provide to the patient are meant to enable him to make his own benefit-risk assessment and agree to the therapy based on his *pharmaceutical informed-consent*.
- In conjunction with other product information texts the PL protects the Marketing Authorisation Holder (MAH) against liability issues.

Due to the New Medicines Legislation (NML), particularly *Directive 2004/27/EC*, PLs have to satisfy two further compulsory aspects:

- They need to be tested in order to ensure their usability and the reports on these tests have to be provided to the competent authorities.
- PLs of decentralised procedures have to be commonly agreed upon by all parties concerned, as it is the case for Summaries of Product Characteristics (SPCs).

The first of the preceding compulsory aspects represents a new obligation. In addition, both aspects also apply retroactively to 'established' MRP products, which is extremely onerous for the pharmaceutical companies.

Pharmaceutical companies have had to develop and implement new processes. In particular, they have to

- make decisions on PL-testing methods and selection of Contract Research Organisations (CROs) in the case of out-sourcing.
- budget for additional funds and personnel.
- acquire knowledge about PL harmonisation and PL-testing.
- integrate the concomitant regulatory procedures into the life cycle of MAs.

The firms involved seek a process which minimizes costs in time and money while satisfying the requirements of regulatory authorities. Towards this end most companies choose the 'Diagnostic Leaflet Testing' method which originated from the Communication Research Institute of Australia (CRIA) as the archetype. Its major advantage is its 'readiness for use', its acknowledgement by European Competent Authorities (CAs), and the availability of CROs that offer this method as a service. Alternate methods are being developed, but mostly at the national level.

Beyond the costs of developing a PL, there are considerable costs in making it suitable for use across the European Union (EU). Additional time and expenditures (CROs, translations, fees) amount to approximately 100,000 - 200,000 € per retroactively harmonised and tested MRP-PL with about 14 countries involved. Knowledge of PL harmonisation and PL-testing increases constantly through 'hands-on' experience, intensive communication with CROs and feedback from authorities during various procedures. It becomes evident that CAs are not prepared any better for the new obligations than the MAHs and generally prefer to come back to established national attitudes. Overall, the new obligations tend to delay the start of

regulatory procedures, particularly in the case of established MRPs, as relevant documentation must be available on Day 0.

PLs change. Based on the *Directive 92/27/EEC* applicable throughout Europe, the anticipation for national PLs of established MRP products was that they would not differ in content but only in language. However, with new Quality Review of Documents (QRD)-templates for decentralised procedures in place and the need for harmonisation, it became obvious that national approaches by companies and CAs differ from country to country. By means of an analysis of PLs from two established MRP products this thesis makes an attempt to categorize these attitudes and provide explanations for CAs' comments during procedures.

As far as the editorial interests of PLs are concerned, there are still many outstanding issues. PL-design, font size, pictograms, and the use of colour are a matter of considerable debate. Due to the lack of 'approved', obligatory, EU-wide demands, only some cautious approaches are being undertaken to use these effective tools in PLs. The adoption of 'ready to use' pictograms is proposed in this thesis.

The last part of this thesis considers the perhaps most promising developments on the horizon for providing more patient-friendly PLs. Such developments involve patient-tailored PLs that meet all of the following requirements: full disclosure, avoidance of liability issues, and being understood by patients. Interestingly enough, the actual way to these patient-tailored PLs would lead back to the initial purpose of a PL, which is, to be a tool for improving doctor/pharmacist-patient communication rather than as a replacement for this dialogue.

6 Appendices

6.1 Appendix 1 - Formal features of European languages

The relationship between the average length of words within a PL, the average amount of words per PL, and the average space needed for the whole PL was exemplarily investigated in the context of translations.

Calculations are based on an English PL, which was translated into the European languages. Only those languages needed in a CP in 2006 were considered. The limitations of the results must not be ignored, as numbers may vary slightly between the texts of different medicinal products. In addition, the numbers vary due to the text type, i.e. for a SPC text the average word length increases by 1-2 characters compared to PL texts. Therefore, only PL texts were analysed to obtain a rough idea of the linguistic aspects of the concerned documents.

The main anticipated impact when transferring a text from English into other languages, such as German, is the **increase in the average length of words**. In the following diagram (Fig. Appendix 1-1) an overview of the average word length in a PL (product F) text is given.

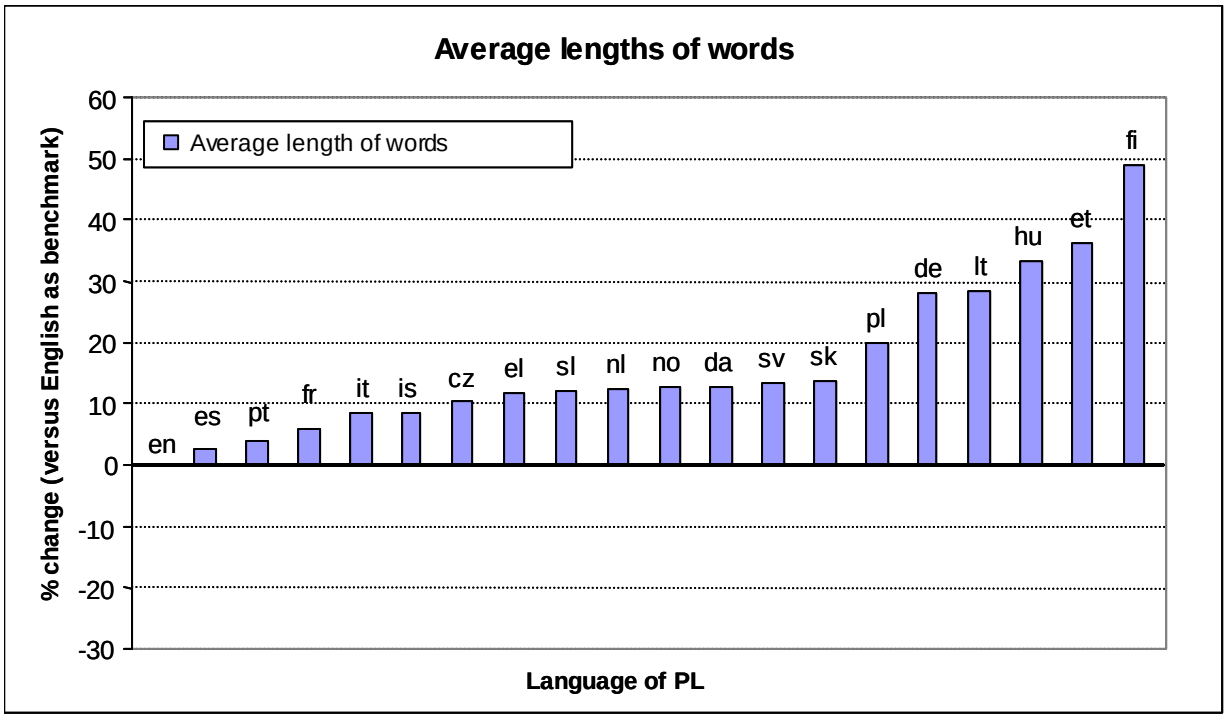


Fig. Appendix 1-1: Diagram of the **average length of words** of an English PL (product F) and its translations into the European languages. Figures ranged from 5.31 characters per word in English to 7.92 characters in Finnish (data not shown). The %-value for English was set as zero. The relationship of the other languages to this is expressed as a % change in comparison to the English benchmark of zero. Abbreviations for languages are according to ISO code 639.[130]

[130] http://www.sil.org/iso639-3/codes.asp (accessed 1. 2.2007)

A different way to present the % change values is to assign the average English word length the value of one and calculate the average word length of each of the other languages in relationship to that as shown below (Tab. Appendix 1-1).

Tab Appendix 1-1: Table shows the change of the average word lengths as presented in Fig. Appendix 1-1. English was used as a benchmark as it is the language of European procedures (CP, MRP). This exercise is mercifully simplified as English has the shortest average word length. F: Factor.

Language	**en**	es	pt	fr	it	is	cz	el	sl	nl
F Word length	**1.00**	1.03	1.04	1.06	1.08	1.08	1.10	1.12	1.12	1.13
Language ctd.	no	da	sv	sk	pl	de	lt	hu	et	fi
F Word length	1.13	1.13	1.14	1.14	1.20	1.28	1.28	1.33	1.36	1.49

The average word length in a certain language does not allow a conclusion about the length of the whole text. For this purpose a second factor has to be taken into account, which is the number of words that is needed to present the same content of a text, i.e. the number of words of a faithful translation (Fig. Appendix 1-2).

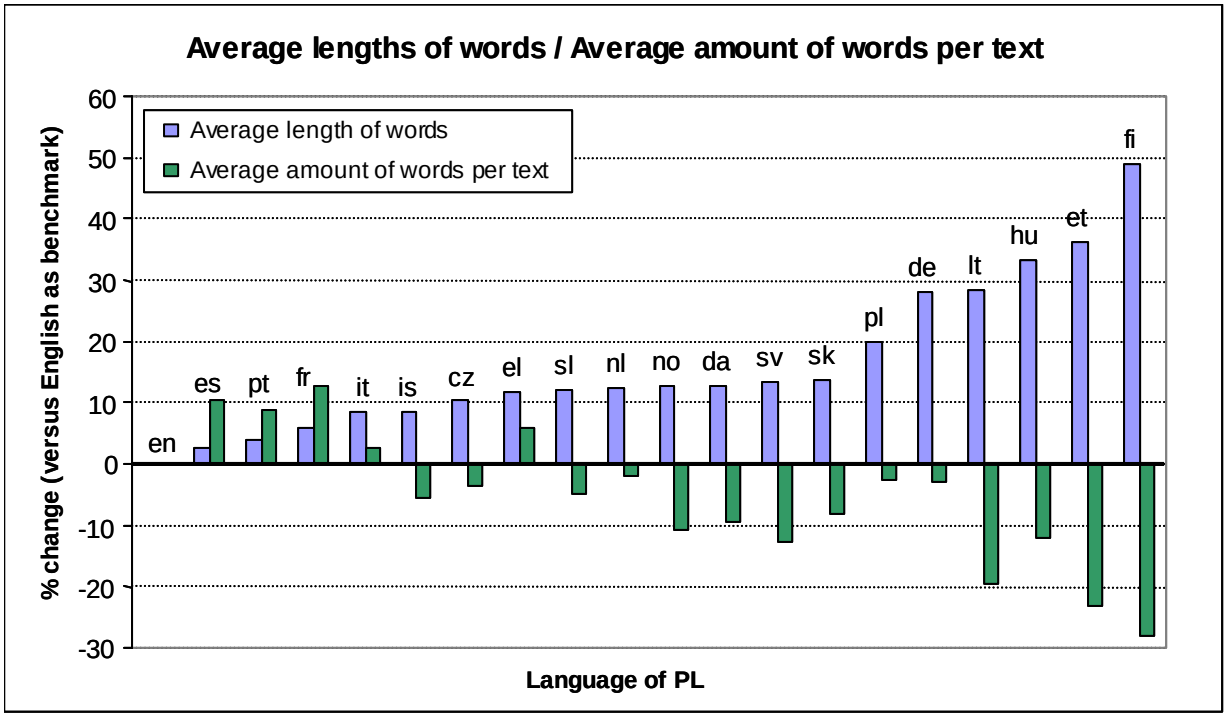


Fig. Appendix 1-2: Diagram of the **average length of words** and the **average number of words** for an English PL and its translations into the European languages. The %-value for English was set as zero. The relationship of the other languages to this is expressed as a % change in comparison to the English benchmark of zero. Figures ranged from 1,410 words in Finnish to 2,214 words in French (data not shown). Abbreviations for languages are according to ISO code 639.[130]

A different way to present the % change values is to assign the average number of English words the value of one and calculate the average number of words of each of the other languages in relationship to that as shown below. (Tab. Appendix 1-2).

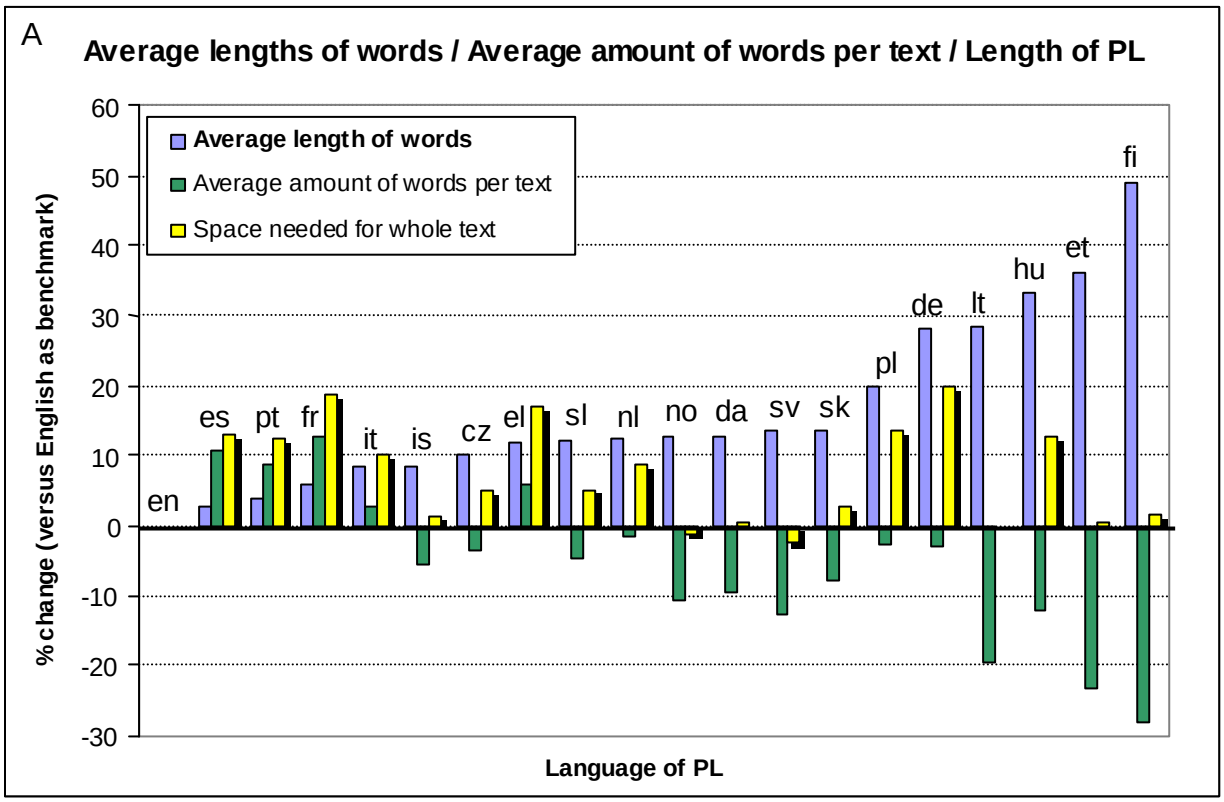
Tab. Appendix 1-2: Table shows the change of the average number of words per text as presented in Fig. Appendix 1-2 (green bars). The order of languages in the table was changed based on the results. F: Factor

Language	fr	es	pt	el	it	**en**	nl	pl	de	cz
F Word/text	1.13	1.11	1.09	1.06	1.03	**1.00**	0.98	0.97	0.97	0.96
Language ctd.	el	is	sk	da	no	hu	sv	lt	et	fi
F Word/text	0.95	0.95	0.92	0.90	0.89	0.88	0.87	0.80	0.77	0.72

There are basically two tendencies when starting from English as benchmark. On the one hand there are languages that have the tendency for longer words as well as for a higher number of words. The most obvious example is French (6 % change in word length and 13 % change in the number of words). On the other hand there are languages that have the tendency for longer words, but compensate with a lower number of words. The most prominent example for this is Finnish (49 % **in**crease in word length and 28 % **de**crease in the number of words).

The actual length (or 'space needed') of a text in a certain language can be estimated from a calculation that takes into account the language specific factors for the average length of words (Tab. Appendix 1-1) and for the number of words per text (Tab. Appendix 1-2).

The result of this calculation might be a bit surprising. The language that needs the most space is neither the language with the longest words (Finnish) nor the language with the highest number of words per text (French). It is a language with considerably long words that also needs nearly as many words per text as the English benchmark. In this example the German version needs the most space (Fig. Appendix 1-3).



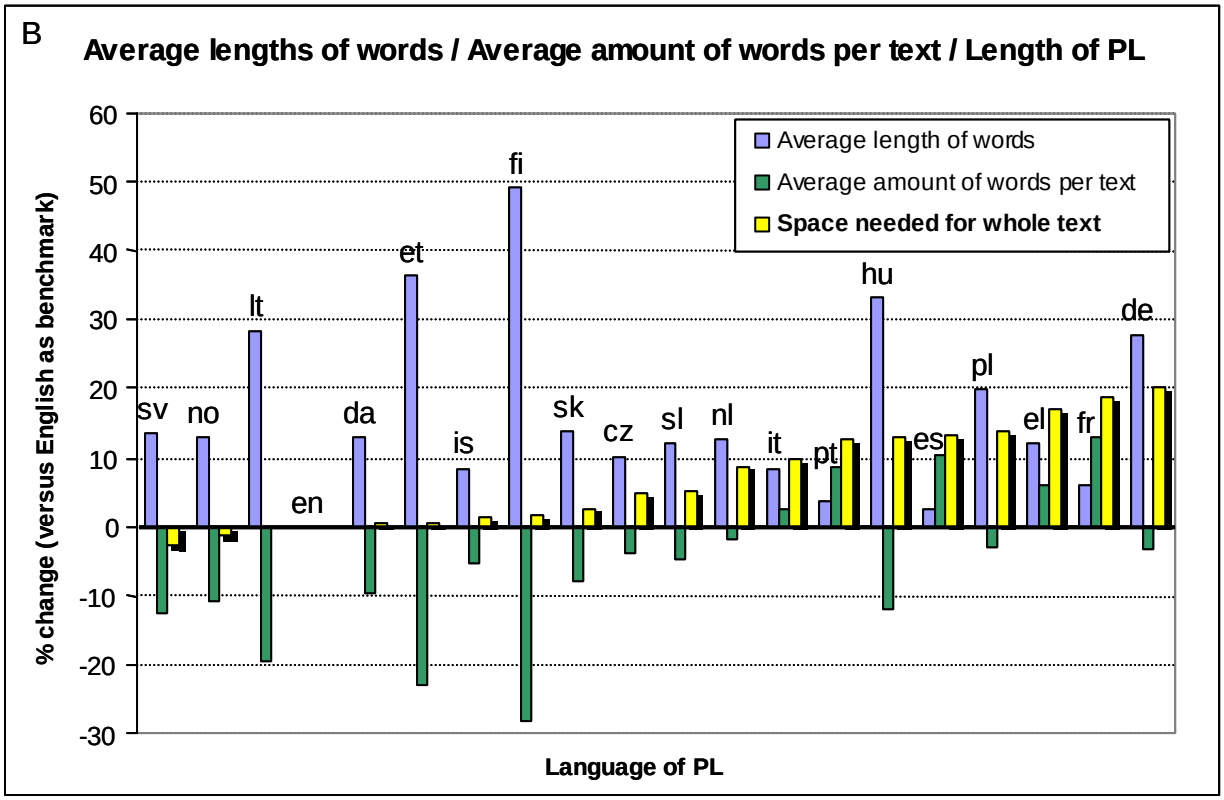


Fig. Appendix 1-3: Diagrams of the **average space needed** for an English PL and its translations into the European languages. Diagram A shows information in the same order of languages as in Figs. Appendix 1-1 and Appendix 1-2. Diagram B sorts the languages by the magnitude of space needed for the whole text. The %-value for English was set as zero. The relationship of the other languages to this is expressed as a % change in comparison to the English benchmark of zero. In absolute number, figures ranged from 11,978 characters (including blanks) in Swedish to up to 14,747 characters (including blanks) in German (data not shown). Abbreviations for languages are according to ISO code 639.[130]

A different way to present the % change values again is to assign the average total amount of space the value of one and calculate the average of each of the other languages in relationship to that as shown below (Tab. Appendix 1-3).

Tab. Appendix 1-3: Table shows the change of space needed for the whole text as described in Fig Appendix 1-3 (yellow bars). The order of languages in the table was changed based on the results. F: Factor

Language	sv	no	lt	**en**	da	et	is	fi	sk	cz
F Space	0.98	0.99	1.00	**1.00**	1.00	1.01	1.01	1.02	1.03	1.05
Language ctd.	sl	nl	it	pt	hu	es	pl	el	fr	de
F Space	1.05	1.09	1.10	1.13	1.13	1.13	1.14	1.17	1.19	1.20

6.2 Appendix 2 - Description of test methods

Test methods were grouped according to the four main test methods for 'Readability':

- Readability formulae / Readability instruments
- Health literacy tests
- Design assessment tools
- Direct patient-PL interaction tests

6.2.1 Readability formulae / Readability instruments

FRE (Flesh Reading Ease Scale)[26]
The FRE, which is also described in the EFPIA recommendations,[17] measures the readability of text written for grade 5 to college graduate level. FRE uses the number of words in a passage and an index of word complexity (based on the number of syllables). At least three text passages (about 100 words each) are needed for testing. Tables and (sub-) headings are excluded. As the score decreases, readability decreases, i.e. the text is more difficult to understand (Scores range from 100 (very easy to read) to 0 (unreadable)). According to EFPIA '*Minimum score for Plain English is 60, or about 20 words per sentence and 1.5 syllables per word*.'

FRE formula:
Score = 206.835 – 1.015 * (words/sentence) – 84.6 * (syllables/word)

FK (Flesh Kincaid scale)[27]
The FK, which is also described in the EFPIA recommendations[17], is in principle a modified version of FRE. It translates the scores obtained with the FRE to a U.S. reading grade level, or to a reading age. EFPIA does not comment on minimum scores.

FK formulae:
Grade level = ((words / sentence) * 0.39) + ((syllables / word) * 11.8) – 15.59
Reading age = ((words / sentence) * 0.39) + ((syllables / word) * 11.8) – 10.59

SMOG (Simplified Measure of Gobbledygook)[28]
The SMOG, which is also described in the EFPIA recommendations,[17] estimates the average school grade of people who could answer 100 % of comprehension questions on the tested passage.[133] It measures the readability of a text based on the total number of polysyllable words (≥ 3 syllables) in 30 sentences of a text. The Reading Grade Level results from the square root of this number and the addition of 3.

SMOG formula:
SMOG RGL = 3 + √ number of polysyllable words in 30 sentences

SMOG was recommended in 1979 by the U.S. National Cancer Institute for the readability assessment of cancer pamphlets.[131]

[131] U.S. National Cancer Institute: HHEW Publication No. 79-1689, Washington DC: Department of Health Education and Welfare. Readability testings in cancer communications; 1979

GFI (Gunning Fog index)[132]
This test was created to estimate the average school grade of people who could answer 90 % of comprehension questions on the tested passage.[133] A passage of about 100 words is analysed by calculating the average length of sentences and the number of complex words, i.e. words with more than three syllables. The average sentence length in words is added to the percentage of complex words. Then the result is multiplied by 0.4. The resulting number is an indication of the number of years of formal education that a person requires in order to easily understand the text at the first reading.

(GFI formula)
GFI = ((words / sentence) + (complex words / words) * 100) * 0.4

Fry (Fry Readability Graph)[134]
This test calculates the average number of sentences and the average number of syllables of a 100 word text passage. Afterwards the result is plotted on the Fry Readability Graph to determine the reading grade level of the assessed text. The Fry Readability Graph plots the average number of sentences per 100 word text (Y-axis) versus the average number of syllables per 100 word text (X-axis) (Fig. Appendix 2-1). Source: Doak CC, Doak GD, Root JH; JB Lippincott Company, Philadelphia. Teaching patients with low literacy skills. 1996

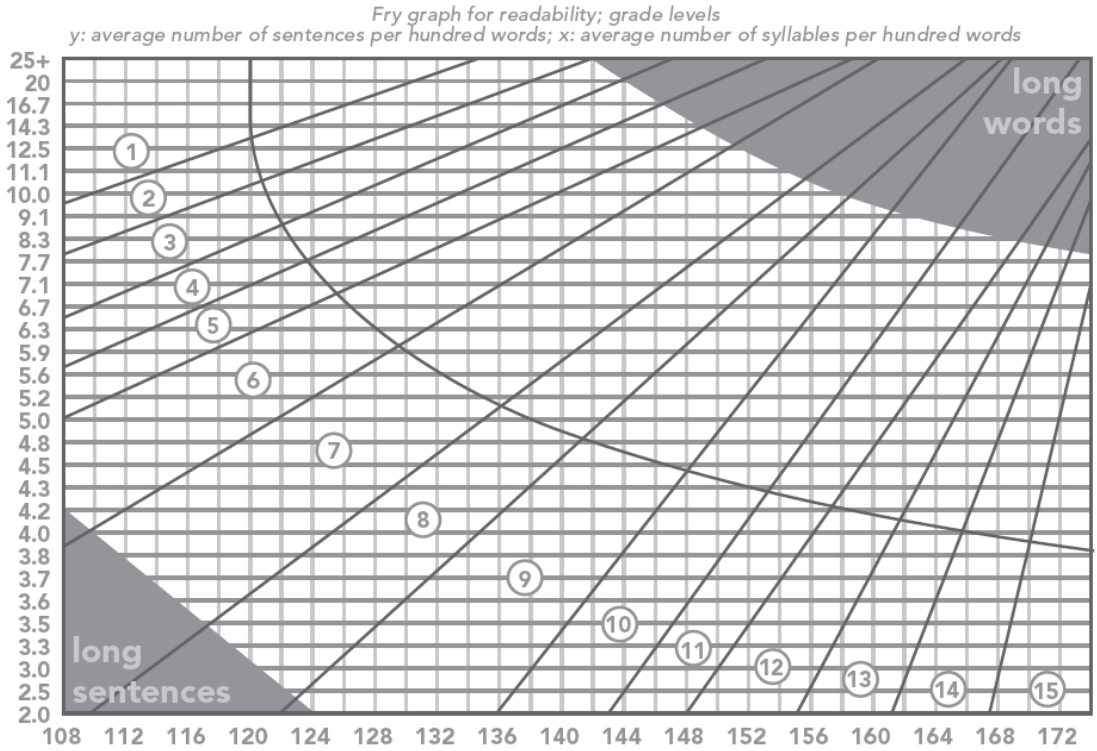


Fig. Appendix 2-1: A rendition of the Fry graph (Source: http://en.wikipedia.org/wiki/Fry_Readability_Formula)

6.2.2 Health literacy tests

WRAT-R (Wide Range Achievement Test - Revised),[29] (available only in English)
This test is a word recognition and pronunciation test. Originally it was established to assess the basic skills of school-aged children and comprised three subtests about reading, spelling

[132] Gunning R: New York: McGraw-Hill. The technique of clear writing; 1968
[133] Ley P, Florio T. Psychology, Health and Medicine. The use of readability formulas in health care; 1996
[134] Fry E: Journal of Reading 11:513-516. A readability formula that saves time; 1968

and arithmetics. After revision in 1987, only the reading part is applied for the purpose of testing (health) literacy. The test can be administered in about 3-5 minutes and evaluates a person's pronunciation of approximately 40 items. It is stopped when the tested person has difficulties with three consecutive words. From the raw score a grade score can be derived. WRAT-R is used in health care settings although it consists of non-medical test words.

REALM (Rapid Estimate of Adult Literacy in Medicine),[30] (available only in English)
This test measures the ability to read and correctly pronounce 66 common medical terms presented in order of increasing syllable number and pronunciation difficulty. REALM is considered more appropriate than WRAT-R. However, the obvious shortcomings for the evaluation of comprehension of health information also holds true for REALM. It may on the one hand overestimate people's reading skills of medical terminology due to excellent pronunciation that goes along with poor comprehension. On the other hand it may underestimate the people's recognition ability because the words are not presented in the context of a text.

REALM-R (Rapid Estimate of Adult Literacy in Medicine - Revised),[31] (available only in English)
This test is a short version of the original REALM. It is composed out of eight medical terms (fatigue, jaundice, directed, allergic, colitis, constipation, anaemia, and osteoporosis). It is applied to quickly screen potential literacy problems in medical settings.

SORT (Slosson Oral Reading test)[135]
This test is also based on a word list like REALM or WRAT. However, there is a series of word lists that are scaled for different grade levels. As SORT needs more procedural steps, it is likely to be more time consuming than the other tests mentioned above.

Cloze procedure[32]
This test, which was developed in 1953, is based on a prose text passage where every fifth word has been deleted. The tested person has to fill in the blanks. If enough words (≥ 50) are deleted by this random procedure, the blanks are intended to represent an adequate percentage of words of varying complexity. There is no predefined text (and therefore no predefined blanks). This test can be applied to any (prose) text. This includes sections of PLs that do not contain tables, word lists, or charts.

TOFHLA (Test of Functional Health Literacy in Adults),[34] (available only in English and Spanish)
This test measures comprehension, including the ability to read and understand both prose passages and numerical information. The estimated testing time per patient is about 22 minutes. There are two sections:

- Reading Comprehension Test (50 items)
  The Reading Comprehension Test has three health related passages (Gunning FOG readability 4.3, 10.4, and 19.5, respectively). In each passage every 5th to 7th word has been deleted. For each blank, the respondent must select from a list of four words the one that completes the sentence in the best way (modified Cloze procedure).

- Numeracy Test (17 items)
  The Numeracy Test assesses quantitative literacy needed in the health care setting. This includes the ability to read and understand numerical information in form of prescription

[135] Slosson RL: Slosson Educational Publications, 538 Buffalo Rd., East Aurora, NY 14052. Slosson oral reading test (SORT) revised; 1990

bottles, appointment slips, or other health-related material. Patients are given to read cue cards or bottles with directions for taking medication and then are orally asked questions about this information. The numeracy items have an average readability of 9.4 according to the Gunning FOG. The 17-items are weighted to yield a Numeracy score of 50.

The complete TOFHLA allows a total of 100 possible points, which represents the sum of numeracy score (up to 50) with the Cloze items (up to 50).

S-TOFHLA (Short Test of Functional Health Literacy in Adults)[33]
This test is similar to the TOFHLA, but reduced to two prose passages (4th and 10th grade level) and 4 Numeracy items. The estimated testing time per patient is about 12 minutes.

6.2.3 Design assessment tools

UFI (User Friendliness Index)[41]
This test was developed by Basara and Juergens as a design evaluation tool. It served as additional tool for the overall assessment of package inserts. The other component was the readability evaluation via a mixture of Readability formulae. For the UFI the design characteristics, such as the use of pictograms or graphics, type size, colour, paper quality, and white space were each scored between one (least preferred state) and three (most preferred state). UFI, which represents the cumulative score indicates the overall design quality. As no 'pass mark' is defined, the UFI can be used to compare PLs against each other rather than to judge the appropriateness of a single leaflet on its own.

BALD (Baker Able Leaflet Design)[42]
This test is based on several publications on design of PLs. It translates the qualitative statements on design requirements to a quantitative measure. Weightings were selected to reflect relative contributions to design according to the author's judgement. The score that can be achieved for a patient information leaflet ranges from zero to a maximum of 32 in this test.

Tab. Appendix 2-1: Baker Able Leaflet Design (BALD) assessment form[42]

Name of CPI		**Value**		
Design characteristics	**3 points**	**2 points**	**1 point**	**0 points**
1. Lines 50-89 mm long			Yes (Y)	No (N)
2. Separation between lines	> 2.8 mm	2.2-2.8 mm		< 2.2 mm
3. Lines unjustified			Y	N
4. Serif typeface		Y		N
5. Type size	≥ 12 point	10-11 point	9 point	< 9 point
6. First line indented			Y	N
7. Titles (headings) lower case			Y	N
8. Italics		0 words	1-3 words	≥ 4 words
9. Positive advice ('Do' instead 'Do not')		Generally positive		Negatives common
10. Headings stand out		Y		N
11. Numbers all Arabic			Y	N
12. Boxed text			0-1 boxes	> 1 box
13. Pictures (not including cover pictures)	Words could not replace	In between	In between	None or superflous
14. Number of colours	4	3	2	1
15, White space (% of page area, e.g. cm^2)	> 40 %	30-39 %	20-29 %	< 20%
16. Paper quality	Thick (> 90 gsm*)	Average (75-90 gsm)		Thin (< 75 gsm)

*gsm – grams per square metre. Standard bond paper or photocopying paper is 80 gsm.

RAIN (Readability Assessment Instrument)
This test method was initially developed to assess the readability of patient information brochures.[43] Its appropriateness to evaluate medication information leaflets was shown by Kirckpatrick and Mohler on seven phenytoin information leaflets.[136] The scoring is based on eight variables that facilitate comprehension:

- **Global coherence**: Paragraphs are scanned for signalling words that indicate structured text such as cause / effect, temporal sequence, compare / contrast, definition / examples, titles, and subtitles.
- **Local coherence**: Paragraphs are scanned for signalling words that indicate clarity of pronoun references, substitutions, and connectives.
- **Unity**: Considering the fulfilment of purpose sentences are identified, which are relevant or irrelevant for the topic.
- **Audience appropriateness**: Evaluation is done on presence and number of new vocabulary, highlighting and definition of new words, as well as the inclusion of synonyms for new words.
- **Adjunct questions**: Evaluation is done on presence and placement of adjunct questions, e.g. appearing as titles or subtitles.
- **Writing style**: Text is scored for active or passive voice
- **Illustrations**: Text is scored for inclusion of photographs, sketches, cartoons, or diagrams; it excludes tables, graphs and charts
- **Typography**: Text is evaluated for font size, font style, colours of paper and print, highlighting for titles and subtitles.

A scoring criterion of 80 % adherence on most variables is considered acceptable by the authors. However, this was not validated.

SAM (Suitability Assessment of Material)[45]
This test was developed by Doak, Doak and Root under the John Hopkins School of Medicine project 'Nutrition Education in Urban African Americans' funded by the National Institutes of Health, National Heart, Ling and Blood Institute, Bethesda, 1993. It mainly consists of 22 SAM factors on a scoring sheet. They are accompanied by a detailed description of the evaluation criteria that have to be fulfilled when the factor is rated to one out of three possible levels. All SAM factors are sorted by 'content', 'literacy demand', 'graphics', 'layout and typography', 'learning stimulation, motivation', and 'cultural appropriateness'. The authors claim SAM to be validated with 172 health care providers from several cultures. However, the data were only presented at a Congress[137] and are not yet publicly available.

MIDAS (Medication Information Design Assessment Scale)[46]
This test allows for an indirect measure of design quality administered by the investigators. A 13-item scale was developed to quantify the extent to which a given leaflet meets various design characteristics as recommended in the 1996 Action Plan of the U.S. Several attributes adapted from the Baker scale. The scoring system assigns one point for the presence of each attribute, with a maximum score of 13. The authors claim MIDAS to be validated, as they assessed the same PLs in parallel with the CIRF method (section 5.2.4), and showed a correlation of results.

[136] Kirckpatrick MAF, Mohler CP. Drug Inf. J 33:557-563. Using the Readability assessment instrument to evaluate patient medication leaflets; 1999
[137] DoakC, Doak L, Miller K, Wilder L. Suitability Assessments of Materials (SAM). American Public Health Association Annual Meeting, Washington, DC; 1. 11. 1994

6.2.4 Direct Patient-PL interaction tests

Diagnostic Leaflet Testing / User testing (MHRA terminology)
This test was developed by Sless and Wiseman at the CRIA.[22,15] The project was initiated by the Australian Health Authority (TGA). There is a series of major consecutive steps for this test method:

- Design and writing of a package leaflet according to the Usability Guidelines[15]
- Format of the text in the layout and on the same paper stock as it will be presented to customers
- Compilation of a tailor-made questionnaire for the leaflet, that reflects the critical actions for the appropriate use of the medicine
- Recruiting of test participants
- Conduction of diagnostic testing (interview) with a first round of ten participants, but only one participant at a time. An explanation is given that it is the package leaflet that is tested, not the participant. The participant is allowed to make himself familiar with the PL, although it is not necessary for him to read all of the text, because he is allowed to use the leaflet for answering the questions. Duration of interview is between 30 and 45 minutes.
- Evaluation of results (comparison with acceptance criteria, section 2.2.2) and adaptation of package leaflet if necessary
- Repetition of diagnostic testing (interview) with another round of ten further participants
- Evaluation …

The cycle of interviews, evaluation and adaptation of the PL is iteratively repeated until the acceptance criteria (section 2.2) are fulfilled for the last 20 tested persons.

The Australian approach was taken up by several European Regulatory guidance documents (section 1.4, section 2.2, and Fig. 1B). MHRA referred to it as 'User testing' and the process was visualised by Paget (Fig. Appendix 2-2).

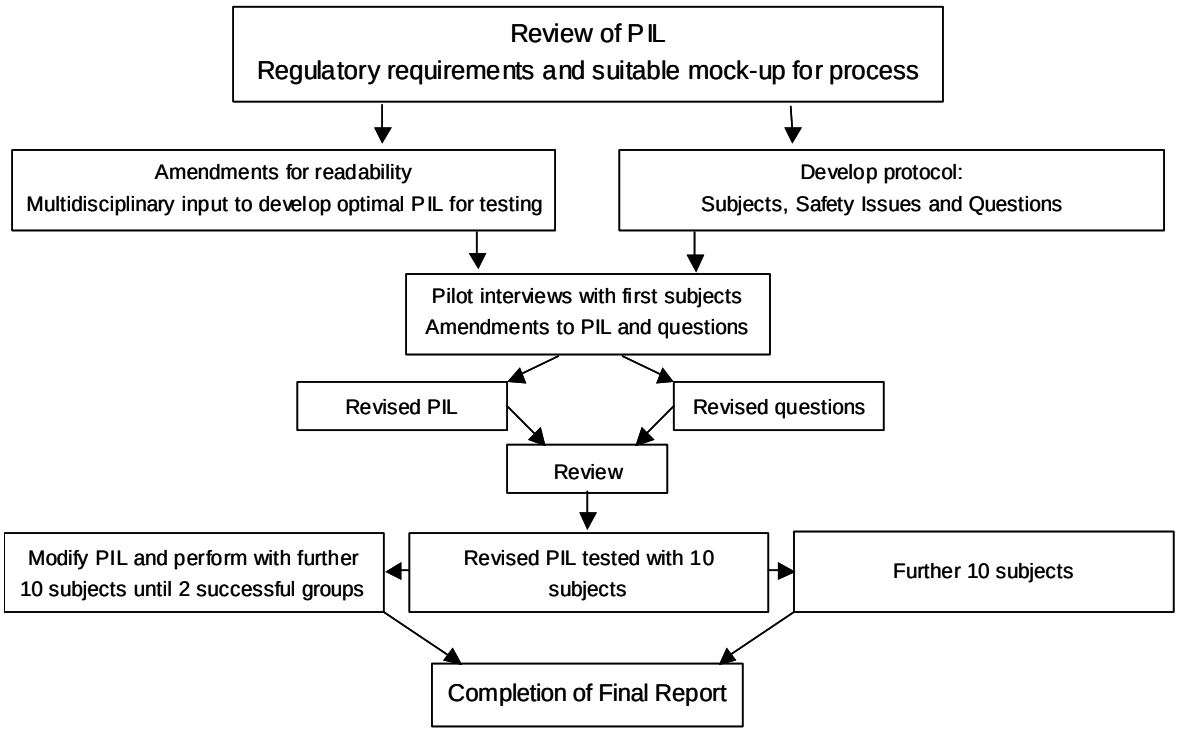


Fig. Appendix 2-2: Process of user testing- as described by T. Paget[138]

[138] Paget T (2006) TOPRA,April, p.14-17. User Testing: Delivering quality in PIL user testing

PAINT / PAckage INsert Test (written readability test) [49,50]
This test, developed by Jörg Fuchs, is based on the Diagnostic Leaflet Test method. The major difference in the conduction of the test relates to the questionnaire about comprehensibility of information provided by the leaflet. This questionnaire is not answered during an interview, but it is a self-administered questionnaire by the patient in writing. The major steps are basically the same as in the Diagnostic Leaflet Testing:

- Refinement of PL according to a list of 104 criteria for quality for PLs
- Conduction of testing with approximately ten participants and a self-administered questionnaire (first test round)
- Evaluation (and refinement of PL if necessary
- Conduction of testing with approximately ten participants and a self-administered questionnaire (second test round)
- Evaluation …

The cycle of refinement, testing, and evaluation is repeated until the pass mark of 80 % correct answers per question is reached for the last twenty participants.

- Report

The self-administered administered questionnaire consists of three major parts:

- Demographic data of participant and self-estimation of existential orientation
- 15 questions on the content of the PL
- Overall judgement on PL by the participant

The type of the content related questions differs from the ones posed during the 'Diagnostic Leaflet Testing':

- They are not tailored to the specific PL under testing. They are generic, i.e. applied to every PL test.
- The topics tackled by these questions are the balanced result of a survey amongst patients about what they think are most important parts of a PL. There is no evaluation of the most critical issues to be asked by the author of the leaflet or HCP.
- To facilitate evaluation each questions is designed to be answered with either 'yes' or 'no', with a single or a few keywords, or a figure.

The author claims to have the test validated[49] as a whole. He also claims that the PAINT consult written readability test received recognition in the MRP in March 2006[139].

CIRF (Consumer Information Rating Form)[46]
This test claims to perform a direct measure of comprehensibility, utility, and overall design quality applied by a consumer panel. It is a two-page self-administered questionnaire that measures the consumer's evaluation of a package leaflet.

The section on comprehensibility points out the major difference between the CIRF-method and the other tests as described in this group of methods with direct patient-PL interaction: Following the CIRF method the patient evaluates five items by scoring them from '1' (very hard) to '5' (very easy). These five items ask (verbatim!) '*how easy or hard'* the PL is to: *read, understand, remember, locate information,* and *keep for future reference*.
This means the test person (the patient) judges by himself on his own ability to locate and understand information from the package leaflet. He does it on his own overall impression about the leaflet, not posing any 'test' questions to himself as a measurement. The CIRF-

[139] http://www.paint-consult.com/uk/aktuell/index.htm (accessed 31. 12. 2006)

method as presented can be used to compare PLs against each other. However, no conclusion was drawn what overall score criteria must be met to claim a package leaflet being 'usable' according to European law.

The authors claim CIRF to be validated, as they assessed the same PLs in parallel with the MIDAS method, and showed a correlation of results.

P.A.P.I. (Psychological Analysis of Patient Information)

The Austrian 'Das Psychotechnische Institut',[53] which has a background in marketing research, particularly on the psychological aspects, developed a PL-testing method that claims to investigate

- the legibility and comprehensibility of a PL **and**
- the emotions of the patient that are triggered by the PL itself and its wording.

Testing is performed by a 'creative group' that '*studies subliminal views and ideas – the emotional, subconscious aspects of a topic – which the participants themselves are not consciously aware of.*' This means images and emotions are uncovered that are developed by the patient, when he reads the PL. Group participants produce drawings and perform role plays according to depth psychology. During these structured group meeting various methods are applied:

- **Group discussions**: The hypothesis is that by group dynamics barriers decrease and the communication is more straightforward and extensive, digging out topics and themes that otherwise would not have come up.
- **Drawings**: This approach uncovers which emotional fields are assigned to the medicinal product under testing.
- **Priority shots**: The complete PL text is highlighted by the interviewee with different colours. Colours are assigned to properties that are attributed by the patient, i.e. congenially perceived text is highlighted in yellow, disagreeable text in green, important text in red, unimportant text in blue, and incomprehensive text in orange.
- **Emotional distance scaling**: This shows the evolved emotional distance that developed between the PL and the medicinal product, or the trademark, or the company.
- **Role plays**: This tool helps to avoid possible personal barriers to express oneself. Participants are asked to play a doctor, explaining the medicinal product, or to play a patient talking about his medicine.
- **Benchmark test**: Image profiles are created by asking the participant about his views about the product and the brand, as well as his readiness to comply with the usage instructions, i.e. participants have to describe their (theoretical) compliance (Q: How long would you take this medicine? A: not at all / until I feel better/ as long as the doctor orders / as described in the PL).

Test results are measured in terms of legibility, comprehensibility, analysis of PL content, emotionality, triggering of fears or non-compliance, perception of single statements, image transfer from PL to medicinal product, image transfer from PL to MAH, and perception of the medicinal product (positioning).

A normal test setting for one PL comprises two groups that meet two hours each, and costs € 4,850.[53]

6.3 Appendix 3 - Assessment criteria at CAs

Overview of assessment criteria at MHRA, BfArM, MEB, AFSSAPS for PLs and/or PL-testing

6.3.1 MHRA (UK)

Assessment protocol for PLs[140]

- Make sure leaflet complies (compatible with SPC, correct order)
- Read leaflet from start to finish
  - Consider layout issues (is it easy to read, is the font large enough, are headings clear)
  - Consider content issue (is the language accessible, is there much jargon, are the risks well explained, is any extra statutory information clear, helpful, and relevant)

Review usability test[140]

- Consider the key safety issues with the medicine. Have these been identified by the applicant?
- Review of the protocol
  - Participants – selection, numbers, age/sex profiles
  - PIL used – must be actual size, colour as in finished pack
  - Questions asked and model answers (random order)
  - Presentation of results
  - Evaluation of results (can patients find and understand the information)
  - Discussion of results and proposals for improvements

Factors which may cause the test to fail[140]

- Failure to question patients about critical safety issues
- Failure to take into account of the views of patients expressed during the test
  - For example if patients are concerned that the size of the text is too small company should increase font size
- Using leading questions or closed questions
- Employing participants who have taken part in a previous test, thereby becoming 'expert' participants
- Allowing too long for the patient to find the information and respond

6.3.2 BfArM (DE)

Assessment of results [141]

Methodology

- Methodology follows readability guideline Annex 2?
- Volunteer population acceptable?
- Quantitative evaluation of responses acceptable?
- Rounds of testing including pilot

Questionnaire

- Number of questions , sufficient?
- Questions cover significant issues?
- Time given to answer acceptable?
- Length of interview acceptable?
- Overall, test meets criteria of 80 % correct answers?

[140] MacDonald J, User testing of PIL's, Management FORUM: What makes a good patient information Leaflet – User Testing – What the MHRA is looking for. 26 January 2006, London

[141] Menges K BfArM im Dialog zur Packungsbeilage im europäischen Kontext und unter Berücksichtigung der neuen gesetzlichen Anforderungen; 15 february 2006, Bonn

- Questions on significant issues meet test criteria of 80 % correct answers?
- Conclusion of applicant accurate?

Resultant layout and design
- Follows general design principles of Readability guideline
- Language includes patient friendly descriptions
- Layout navigable
- Use of diagrams acceptable

6.3.3 MEB (NL)

Criteria for the assessment of a package leaflet readability test after 1 Nov. 2005 [142]

Test subjects
- How many **test subjects (ts)** participated?
- Is the number of ts sufficient?
- Is it clear how the test subjects were approached?
- Is it clear that the group of ts was put together adequately?

Methodological choices
- Are the questions formulated adequately?
- Has the text been evaluated in sufficient detail?
  - were there at least 15 questions covering the relevant passages in the package leaflet?
  - were there also questions of a more open nature regarding positive and negative aspects?

Data handling
- Are all appendices present?
- Are the data processed adequately?

Diagnostic quality
- Are the results clearly linked to the three quality aspects:
  - traceability
  - comprehensibility
  - applicability
- Has attention been paid to problems, errors and misunderstandings of the test subjects in the case of a diagnostic test?

In the case of a problem seeking or diagnostic test:
- Did the results lead to sufficient revision?
- If so, have the revisions been justified in terms of the intermediate results?

In the case of final assessment (not compulsory)
- Has a norm been set?
- If so, was is the norm and was it achieved?

Conclusions
- Are the conclusions reported in a clear, concise and well-organised way?
- Have the recommendations and conclusions also been incorporated in a revision of the text?
- Does the test give the impression that
  - the traceability of the product information in the package leaflet is good/improved?
  - the comprehensibility of the product information in the package leaflet is good/improved?
  - the applicability of the product information in the package leaflet is good/improved?

[142] http://www.cbg-meb.nl/uk/reghoudr/index.htm (accessed 21 Januar 2007)

6.3.4 AFSSAPS (FR)[143]

User testing

A Technical assessment

- Recruitment
  Is the recruitment method well defined? What data are known about the volunteers?
- Questionnaire
  How many specific questions were applied? How many general questions? Did the specific questions cover the key issues of the PL? Does the wording of the questions repeat the wording used in the PL?
- Time aspects
  How long did the interviews last? Are real time data for the interviews provided?
- Procedural aspects
  How many rounds of interviews took place? How many participants were involved? Have there been changes to the PL between interview rounds to maximise readability?
- Interview aspects
  Did interviewees receive a full-sized sample of the PL for the test? What instructions were given to the interviewer?

B Evaluation of the responses

- Evaluation system
  Were questions designed to determine whether users can identify key information that is necessary to ensure the appropriate use of the product?
- Question rating system
  How was the ease of location scored? How is the pass criteria defined?
- Data processing
  How are responses recorded? In writing, in audio and/or video recording?

C Assessment of the Report and the Test

- Quality aspects
  - Evaluation of diagnostic questions
    How detailed is the rating system on understanding? Did all questions exceed the criteria of 80 % correct answers? Were all questions easy to locate?
  - Evaluation of layout and design
    Were mock-ups provided? How did the test subjects like the layout?

- Diagnostic quality/evaluation
  - Was the PL amended to improve the quality according to the test results?

Package leaflet

Regarding drug-drug interactions, the current QRD template proposed to describe, in the section 'Taking / using other medicines', the effects of other products on the product in question and vice versa and reference should be made to the intensification/weakening and the extension/shortening of effects.
The AFSSAPS does not exactly share the same view regarding this proposal and highlights the fact that the package leaflet is to be addressed, above all, to the patients. The latter are neither physician nor pharmacist and in never case they should decide on the continuation or the withdrawal of their other current treatments. In this way, regarding drug-drug interactions, the given information in the package leaflet should be essential, simple, clear and pragmatic and not long, not confusing, possibly leading a lack of patient's compliance.

[143] This information is not yet publicly available. Conclusions on assessment criteria from AFSSAPS can only be drawn from actual PVARs and FARs. In this case this deduction was drawn from two examples.

Therefore, the AFSSAPS suggests limiting the redaction of the package leaflet to:

- *Combinations contraindicated with a cross reference in section 'Do not take or use X '*
- *Combinations not recommended with a cross reference in section 'Take special care'*
- *A short but powerful paragraph that warns the patients about a potential risk with other medicines. This strongly insists the patients to ask or warn his physician or pharmacist about his other current co-medications. Only physicians are able to decide whether these other medicinal products, or the product itself, should be continued, withdrawn or the dosage be adjusted.*

6.4 Appendix 4 Abbreviations

ABPI	The Association of the British Pharmaceutical industry
AIGA	American Institute of Graphic Arts
AJATA	All Japan Airport Terminals Association, Inc.
AMG	Arzneimittelgesetz
AOK	Allgemeine Ortskrankenkasse – Die Gesundheitskasse
AT	Austria
AU	Australia
BALD	Baker Able leaflet Design
BE	Belgium
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BG	Bulgaria
BGMA	British Generic Manufacturing Association
BPG	Best Practice Guide
CA	Competent Authority
CD	Council Directive
CIRF	Consumer Information Rating Form
CMD(h)	Coordination group for Mutual recognition and Decentralised procedures - human
CMI	Consumer Medicine Information
CMS	Concerned Member State
CPI	Consumer Product Information
CRIA	Communication Research Institute of Australia
CRO	Contract Research Organisation
CP	Centralised Procedure
CTD	Common Technical Document
CY	Cyprus
CZ	Czech Republic
DCP	DeCentralised Procedure
DK	Denmark
EC	European Community
EE	Estonia
EEC	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Tree Trade Association
EGA	European Generic medicines Association
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
ES	Spain
EU	European Union
FI	Finland
FR	France
DE	Germany
FRE	Flesh Reading Ease Scale
Fry	Fry Readability Graph
FK	Flesh Kincaid scale
GFI	Gunning Fog Index
GL	Guideline
GR	Greece
HCP	Health Care Professional
HU	Hungary

HQ	Headquarters
ICH	International Conference on Harmonisation
IE	Ireland
IMB	Irish Medicines Board
INN	International Non-proprietary Name
IS	Iceland
ISO	International Standards Organisation
IT	Italy
LV	Latvia
LT	Lithuania
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board (Dutch Health Authority)
MedDRA	Medical Dictionary for Regulatory Affairs
MFRG	Mutual Recognition Facilitation Group
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MIDAS	Medication Information Design Assessment Scale
MRP	Mutual Recognition Procedure
MS	Member State
MT	Malta
NtA	Notice to Applicants
NL	The Netherlands
NML	New Medicines Legislation
NO	Norway
PAINT	PAckage INsert Test
P.A.P.I	Psychological Analysis of Patient Information
PI	Physician's Information / Package Insert (U.S. terminology)
PIM	Product Information Management
PIL	Patient Information Leaflet (term for PL used in UK)
PL	Package Leaflet
PL	Poland
PPI	Patient Package Leaflet (British terminology)
PT	Portugal
PVAR	Preliminary Variation Assessment Report
OTC	Over The Counter
Q	Question
Q&A	Question and Answer
QRD	Quality Review of Documents (group)
RAIN	Readability Assessment INstrument
REALM(-R)	Rapid Estimate of Adult Literacy in Medicine(-Revised)
RMS	Reference Member State
RO	Romania
RSI	Request for Supplementary Information
SAM	Suitability Assessment of Material
SE	Sweden
SOC	System Organ Class (MedDRA terminology)
SORT	Slosson Oral Reading test
SPC	Summary of Product Characteristics
SPL	Structured Product Labeling
(S-)TOFHLA	(Short) Test Of Functional Health Literacy in Adults
SK	Slovak Republic

SMOG	Simplified Measure Of Gobbledegook
SI	Slovenia
SUKL	Státní ústav pro kontrolu léčiv - State Institute for Drug Control
TOFHLA	Test Of Functional Health Literacy in Adults
TGA	Therapeutic Goods Authority (health authority in Australia)
UK	United Kingdom
UFI	User-Friendliness-Index
U.S.A.	United States of America
VZBV	Verbraucherzentrale Bundesverband
WHO	World Health Organisation
WidO	Wissenschaftliches Institut der AOK
WMP	Writing about Medicines for People
WRAT –R	Wide Range Achievement Test – Revised
ZA	South Africa

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