

The impact of the revised EU-legislation concerning
particular needs of blind and partially-sighted patients
and user testing – a challenge for pharmaceutical
companies with focus on Germany

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Abbreviations

AMG	Arzneimittelgesetz (Medicinal Products Act; The German Drug Law)
AOK	Allgemeine Ortskrankenkasse (Statutory health insurance fund)
AR	Assessment Report
BAH	Bundesverband der Arzneimittel-Hersteller e.V. (German Medicines Manufacturers' Association)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BGG	Behindertengleichstellungsgesetz (Equality law for disabled persons)
BITV	Barrierefreie Informationstechnik-Verordnung (Barrier-free communication technology regulation)
Blista	Deutsche Blindenstudienanstalt e.V. (German Study Institute for the Blind in Marburg)
BPI	Bundesverband der Pharmazeutischen Industrie e.V. (German Association of Pharmaceutical Industries)
CBG MEB	College Ter Beoordeling Van Geneesmiddelen - Medicine Evaluation Board (The Netherlands)
CMD(h)	Coordination Group for Mutual Recognition Procedures and Decentralised Procedures (human)
CMS	Concerned Member State
CP	Centralised Procedure
CRO	Contract Research Organisation
CTD	Common Technical Document
DAISY	Digital Accessible Information System
DAZ	Deutsche Apotheker Zeitung (German Journal for Pharmacists)
DBSV	Deutscher Blinden- und Sehbehindertenverband e.V. (The German Federation of Blind and Visually Impaired People)
DCP	Decentralised Procedure

DIN	Deutsches Institut für Normung e.V. (German Standards Institute)
DTD	Document Type Definition
DZB	Deutsche Zentralbibliothek für Blinde (German Central Library for Blind)
EAN	International Article Number (former: European Article Number)
EEC	European Economic Community
EBU	European Blind Union
EC	European Community
EU	European Union
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
FDA	Food and Drug Administration
FI	Fachinformation (German Summary of Product Characteristics)
g	gram
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HWG	Heilmittelwerbegesetz (Law concerning Advertising in the Health Care System)
IMB	Irish Medicines Board
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISO	International Organisation for Standardisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
min	minute
ml	millilitre

MP3	MPEG-1 Audio Layer 3 (Digital audio encoding format); MPEG (Moving Picture Experts Group)
MRP	Mutual Recognition Procedure
NHS	National Health Service
OTC	Over the counter
pdf	Portable Document Format
PIF	Pharma Industry Finland (Finish association of the research-based pharmaceutical industry)
PIL	Patient Information Leaflet ¹
PIM	Product Information Management
PL	Package Leaflet
PSUR	Periodic Safety Update Report
pt	Point (font size)
PZN	Pharmazentralnummer (German Article Number)
Q+A	Questions and Answers
QRD	Quality Review of Documents
RFT	Rich Text Format
RLS	Rote Liste [®] Service GmbH
RMS	Reference Member State
RNIB	Royal National Institute of the Blind
SME	Small and Medium-Sized Enterprises
SmPC	Summary of Product Characteristics
SOC	System Organ Class
UK	United Kingdom
WIdO	Wissenschaftliches Institut der AOK (Scientific Institute of AOK)
VFA	Verband Forschender Arzneimittelhersteller e.V. (German Association of Research-Based Pharmaceutical Companies)
vs.	versus
XHTML	Extensible Hypertext Markup Language

¹ The expressions Patient Information Leaflet (PIL) and Package Leaflet (PL) will be used interchangeably.

XML	Extensible Markup Language
ZAPP	Zentrum für Arzneimittelinformation und Pharmazeutische Praxis (Centre for Drug Information and Pharmaceutical Practice)

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1 INTRODUCTION

With the implementation of Directive 2004/27/EC, amending the European Directive 2001/83/EC [1], far-ranging revisions have been established in terms of the marketing authorisation procedures but also with regard to the rules on packaging in order to ensure the proper use of medicinal products.

The main focus of the present master thesis is to provide an overview of the regulatory changes implemented in Europe for the Braille requirements for labelling and the package leaflet to address the particular needs of blind and partially-sighted patients. Secondly, a review of the newly introduced obligatory consultation with target patient groups for package leaflets is presented. In principal, it is focused on the situation in Europe with particular attention to Germany, describing the status as of spring 2007.

Based on a presentation of the current European regulatory provisions and recently published proposals for additional guidance in Europe and especially in the United Kingdom, a critical evaluation including fields for improvement and for further European harmonisation will be given.

The first part of this thesis deals with the Braille requirements for labelling in Europe and details the current status of implementation especially in Germany including particular facilitations and exemptions introduced for the German market. The different steps when implementing Braille labelling on the packaging materials in a pharmaceutical company and the respective challenges especially with regard to the variable special characters in Braille for European languages are presented. Implications on the outer packaging materials, their manufacture and release procedures are described as part of a proposed workflow for a marketing authorisation holder.

Furthermore, potential approaches for implementation of the requirement of making available package information leaflets in formats appropriate for the blind and partially-sighted are discussed. The proposed project of the Rote Liste[®] Service GmbH for the German market is presented and evaluated taking into consideration the systems that have already been implemented in the United Kingdom, the Netherlands and Sweden.

The second part gives an overview of the historical background of package leaflets, their purpose and the main objections and problems encountered in the past. Having summarised the main items of the so-called “readability guideline”, a thorough description and critical evaluation of the major steps of the consultation with target patient groups by interview technique based on the “Australian method” is illustrated.

Alternative methods for testing are presented and assessed for their applicability and potential weaknesses. Options for waivers and bridging studies to reduce the number and extent of user consultation are challenged.

Finally, additional fields for general improvement of package leaflets and critical items as detailed in the so-called “readability guideline” are discussed including an evaluation of further points to be considered for enhancing the overall perception and value of patient information leaflets.

2 BRAILLE REQUIREMENTS FOR LABELLING AND THE PACKAGE LEAFLET

2.1 Regulatory background

Several changes to the rules on packaging have been implemented as part of the Directive 2004/27/EC, amending Directive 2001/83/EC, in order to ensure the proper use of medicinal products. The legal text of Directive 2001/83/EC, as amended by Directive 2004/27/EC, Article 56a is as follows: “*The name of the medicinal product, as referred to in Article 54, point (a) must also be expressed in Braille format on the packaging. The marketing authorisation holder shall ensure that the package information leaflet is made available on request from patients’ organisations in formats appropriate for the blind and partially-sighted.*” Article 54a of the said Directive details: “*The name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults; where the product contains up to three active substances, the international non-proprietary name (INN) shall be included, or, if one does not exist, the common name.*” [1].

The provision of Article 56a applied to all medicinal products approved after 30 October 2005, i.e. after the end of the implementation period of the amended Directive. It did not apply immediately to products authorised before 30 October 2005. Transposition of the Directive in national legislation of the European member states has to be taken into account for specific implementation requirements.

The guidance concerning the Braille requirements for labelling and the package leaflet, dated 2005 [2], which now forms part as chapter 2 of the Draft Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use, [3] details that the (invented) name of each medicinal product followed by its strength should be put in Braille on the packaging of the product. The name of the product may be either an invented name or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder. For medicinal products authorised only in a single strength, it is acceptable that only the invented name in Braille is put on the packaging.

The interpretation as stated in the guidance does not prevent companies to express additional information in Braille such as pharmaceutical form, and if appropriate, whether it is intended for babies, children or adults, etc., especially with regard to bigger volume packages. In addition, the inclusion of the expiry date in Braille is also encouraged.

The guidance further details specific requirements:

- Herbal Medicinal Products: The Braille requirement will be restricted to the invented name of the medicinal product only².
- Small volume packages (i.e. up to 10 ml, with limited space capacity): Alternative means of providing Braille information may be considered, e.g. use of contracted Braille system or certain defined abbreviations or addition of supplementary “tab” label.
- Multilingual packaging: The name in Braille has to be printed in all different languages concerned.
- Products intended for administration by health care professionals only: There is no need to put the name in Braille on the packaging of these products, e.g. vaccines.

2.2 The Braille alphabet

Braille is the internationally widespread reading and writing system for blind and partially-sighted people. The system was founded in 1825 by Louis Braille (1809 – 1852), who himself was blind.

Louis Braille was born in 1809 in Coupvray near Paris, France, but he spent most of his childhood in Lisle. His father, Simon-René Braille, was a harness and saddle maker. As a small boy, he crept into his father’s workshop to play and to try making shoes as his father did. He picked up an awl, a sharp, pointed tool used for making holes in leather. As he bent over, the awl slipped and pierced his eye, destroying it forever. Some time later his other eye became infected by the first and he lost his sight altogether at the age of four.

At the age of seven, Braille earned a scholarship to the Institution Royale des Jeunes Aveugles (Royal Institution for Blind Youth) in Paris, one of the first of its kind in the world. At school, the children were taught basic craftsman’s skills and simple trades, but were also taught how to read by feeling raised letters (a system devised by the school’s

² If the name consists of the active substance(s), information may be limited to the plant name (+ plant part in those cases where several parts are available), plus the type of preparation and the strength in those cases where several strengths exist.

founder, Valentin Haüy). However, because the raised letters were made using paper pressed against copper wire, the students never learned to write.

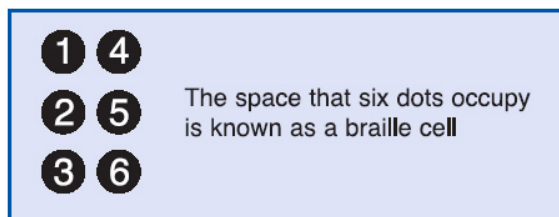
In 1821, Charles Barbier, a former soldier, visited the school. Barbier shared his invention called “synography”, a code of 12 raised dots and a number of dashes that let soldiers share top-secret information on the battlefield without having to speak.

Based on this system, Louis Braille began inventing his raised-dot system with his father’s stitching awl. His system used only six dots and corresponded to letters. The six-dot system allowed the recognition of letters with a single fingertip. These dots consisted of patterns in order to keep the system easy to learn and including the ability to both read and write an alphabet.

Braille later even extended his system to include notation for mathematics and music [4, 5].

The Braille alphabet is based on six dots, with two columns of three dots, which form the so-called Braille cell. Numbering of the dots is defined as depicted in *Figure 2-1*.

Figure 2-1: Braille cell



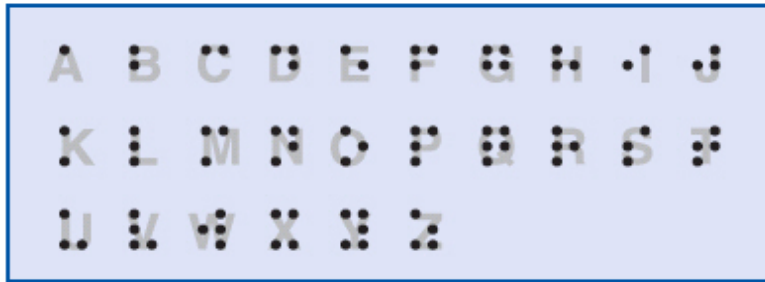
Variations of the risings of these six dots represent all the letters of the alphabet, punctuation and groups of letters. Overall 63 combinations of these six dots exist. The standard Braille alphabet, which is commonly used within Europe, is shown in *Figure 2-2*. The reading direction of the Braille is the same as the regular type. Rules for hyphenation are applied as in regular type, i.e. with hyphenation lines.

Figure 2-2: Braille standard alphabet

A	B	C	D	E	F	G	H	I	J
⠠	⠡	⠢	⠣	⠤	⠥	⠦	⠧	⠨	⠩
K	L	M	N	O	P	Q	R	S	T
⠠	⠡	⠢	⠣	⠤	⠥	⠦	⠧	⠨	⠩
U	V	X	Y	Z	W				
⠠	⠡	⠢	⠣	⠤	⠥	⠦			

Although Braille is made up of dots and not lines, there are at least some similarities with print letters, which help finding patterns when learning the Braille alphabet (see *Figure 2-3*) [6].

Figure 2-3: Braille alphabet and similarities with print letters



2.3 Status of implementation at European member state level

As explained above, the provisions of Article 56a of Directive 2001/83/EC, as amended by Directive 2004/27/EC, detailing the Braille requirements on the packaging of medicinal products applied after the end of the implementation period of the amended Directive, i.e. 30.10.2005 (see section 2.1 *Regulatory background*). Despite of this implementation period not all member states have yet adapted their national drug law to reflect these provisions of the European Directive.

The status of implementation as per 13 March 2007 of the Braille requirements on the outer packaging and the availability of package leaflets for blind and partially-sighted patients are detailed in *Appendix 1*.

2.3.1 Status of implementation of Braille labelling in Germany

Germany already included the Braille requirements with the 12th and 12ath amendment of the German Medicinal Products Act (AMG), dated 30.07.2004 and 15.04.2005, respectively [7]. According to the German Drug Law (AMG), § 10 (1) 2, the labelling must include "... *the name of the medicinal product, followed by details of the strength and pharmaceutical form and, if applicable, information stating that it is intended for administration to babies, children or adults unless this information is already included in the name...*". Furthermore, § 10 (1b) AMG details the Braille requirements on the outer packaging for medicinal products for human use. The name of the medicinal product has to be stated in Braille on the outer packaging. Details on the pharmaceutical form and

the group of persons for which the medicinal product is intended are not required even if they form part of the name of the product³ [8].

In accordance with the European provisions, Braille labelling is not required for medicinal products in Germany, which are intended for use by health care professionals only and which, on the other hand are not feasible for adequate use of blind and partially-sighted patients, e.g. vaccines, radiopharmaceutics, parenteral solutions for infusion, etc. Furthermore, these exceptions pertain to clinical packs as well as bundle packs or transportation packs as these are not handed directly to patients.

In contrast to the European provisions the German Drug Law, however, explicitly excludes medicinal products presented in volumes with a nominal capacity of less than 20 ml or 20 g from Braille labelling. The dimensions of the Braille spots have to follow certain requirements to ensure the readability and palpability of the Braille labelling on the outer packaging. Consequently, adequate measurements of the secondary packaging materials are needed (see section 2.4.1.4 *Requirements for Braille on folding cartons (technical aspects)*). Pack sizes however have to be chosen in accordance with their content, i.e. enlargement of the folding carton is not allowed due to legal competition law to avoid any fraud [9]. Consequently, the lower level of pack sizes limiting the need of Braille labelling in Germany can be considered a well-balanced compromise between the demands of blind and partially-sighted patients and the technical feasibility for pharmaceutical manufacturers on the other hand.

2.3.1.1 Transition provisions

Transition provisions concerning Braille labelling have been detailed in the German Drug Law, 12th amendment, § 138. Medicinal products authorised prior to 30.10.2005 must comply with the Braille provision by the next renewal of the marketing authorisation or at latest by 30.10.2007 (§138 (7) AMG). The Braille provision has to be fulfilled starting from 01.09.2006 to all marketing authorisations granted after 30.10.2005. Product packages already placed on the market prior to these implementation dates without Braille may be marketed unlimited by wholesalers and retailers⁴.

³ In the period of preparation of the 12th amendment of the German Drug Law, it was even proposed to include Braille labelling on primary packaging materials also, such as blister strips, and to fix shorter transition periods. These proposals have not been implemented in the German Drug Law due to the intervention of the German pharmaceutical associations, especially the “Bundesverband der Pharmazeutischen Industrie” (BPI). Implementation of Braille labelling on primary packaging materials would not have been feasible with reasonable efforts as the Braille dots will most likely be damaged when withdrawing a tablet or capsule from the blister strip, etc.

⁴ Prior to implementation of the 12th amendment of the German Drug Law, all pharmaceutical preparations not arranged with Braille labelling as of 01.09.2006 would not have been legally marketable but would have needed a recall, which in fact, could not be explained by safety or any comparable profound reason.

Although these transition provisions seem feasible, there may be distinct situations where it is rather impossible to follow these. For any medicinal product for which a renewal is granted in the time period between 01.09.2006 and 30.10.2007 (i.e. the date where all marketed products with marketing authorisations granted prior to 30.10.2005 have to comply with the Braille provisions) immediate adjustment of the packaging materials would be needed. As this is not manageable in practice and as an estimation of the date of receiving the renewal document on the other hand is impossible, marketing authorisation holders have to implement the Braille provisions for those products in question already before the deadlines indicated above. A common implementation date as of 30.10.2007 for all products authorised prior to 30.10.2005 would surely have also been of benefit for the patient population in question and would have led to more planning flexibility for the marketing authorisation holders.

A further potential approach would be to equip already manufactured and packaged medicinal products with transparent adhesive stickers bearing the appropriate Braille labelling as an additional manufacturing step (see section 2.4.1.4 *Requirements for Braille on folding cartons (technical aspects)*). This is also a helpful tool to avoid unnecessary destruction of already existing stocks of folding cartons.

2.3.1.2 Facilitations according to German Drug Law

In general, the 12ath amendment of the German Drug Law comprises a number of exceptions for marketing authorisation holders, e.g. with respect to unlimited marketing of product packages placed on the market without Braille prior to the above mentioned implementation dates as opposed to the necessity of recalls of all these packages from wholesalers and pharmacies. The same applies to waivers for products exclusively used and applied by health care professionals only as well as for small pack sizes of not more than 20 ml or 20 g (the latter being more tolerant than the respective European regulations). This exemption, however, is heavily criticised by the German Federation of Blind and Visually Impaired People (DBSV) since especially eye drops that are used by blind people on a daily basis are not required to be labelled with Braille [10].

Homoeopathic medicinal products, which are registered only (§ 10, (4), 2nd sentence AMG), are exempted from Braille labelling as well [11].

Furthermore, the German Federal Ministry of Health has issued an additional regulation, the Regulation on labelling of medicinal products with Braille for midget amounts (Braille – midget amounts – regulation, dated 14.07.2006 [12]), detailing exemptions from Braille labelling for medicinal products, which are manufactured in quantities of not more than 7000 packages per year. The regulation is based upon § 12 (1), 1, no. 2, AMG, empowering the Federal Ministry of Health for implementation of regulations to provide the particulars for labelling by other means. The respective marketing authorisation

holder, however, has to deliver the required Braille labelling on separate information sheets or adhesive labels in case of dispensing the product to blind or partially-sighted patients in a pharmacy.

This national regulation enables especially pharmaceutical companies offering homoeopathic and anthroposophic medicinal products or any medicinal products manufactured in small amounts only to make the preparations available on the market. In particular for homoeopathic preparations the secondary packaging, i.e. the folding carton, is - due to the huge variety of preparations - usually printed online during the final packaging process as these preparations are often manufactured on distinct orders only but not in advance. Consequently, the commensurability of pharmaceutical regulations and the existence of a broad variety of pharmaceutical preparations have to be mutually balanced. Implementation of the German Braille – miget amounts – regulation in fact ensures the future availability of pharmaceutical products in Germany also with acceptable additional burdens for the concerned pharmaceutical manufacturers.

2.3.1.3 Marburg Medium for Braille characters

A draft standard DIN 55561 “Packaging – Braille on Labelling” was published in June 2006 as a code of practise for the standardised fabrication of Braille on packaging. These rules have been developed as a basis for the technical implementation of Braille as well as a recommendation for a secure and unobstructed sequence of steps from the creation of the artwork files up to the delivery of the packaging [13]. For the German-speaking areas the “Braille commission of the German speaking countries” has defined the rules for Braille. The system which was agreed in 1998 is available in written form [14].

The basic system of Braille is the so-called “uncontracted Braille” or Braille level 1, it is a repetition of a text in 6-dot-Braille without abbreviations, i.e. each individual letter of the alphabet, punctuation mark, etc. is represented by its own Braille character(s). In addition, the German Braille system, however, has implemented abbreviations for certain, very frequently used phonetic groups, such as “au, äu, ch, ei, eu, ie, sch” and “st”, the so-called “full scripture / full type”. These abbreviations are used only where these combinations of characters are spoken in sequence. Both systems are described in “Das System der Deutschen Blindenschrift” and can be used for German-speaking regions [14]. In contrast, the European “Guidance concerning the Braille requirements for labelling and the package leaflet” [2] as well as the “Guidelines to European Pharmaceutical companies and distributors / marketing agencies” [15] recommend the use of the uncontracted Braille, i.e. the basic system. For further differences concerning the implementation of Braille in the different European member states and the

respective implications for pharmaceutical companies see section 2.4.1.2 *Nationally different special characters in Braille for European languages*.

2.4 Implementation of Braille on the packaging in the pharmaceutical industry

2.4.1 Preparation of Braille labelling on the packaging

The implementation of the Braille requirements in the various European member states is in line with the recommendations of the European “Guidance concerning the Braille requirements for labelling and the package leaflet” [2] as well as the “Guidelines to European Pharmaceutical companies and distributors / marketing agencies” [15] (see *Appendix 1*). Only a few countries have implemented additional specific national features, such as the mandatory use of “Code Antoine” in France, the acceptable use of “Code Antoine” in Belgium, the use of Marburg Medium with special Hungarian characters in Hungary and the use of the “full scripture / full type” Braille system in Germany (see section 2.3.1.3 *Marburg Medium for Braille characters*).

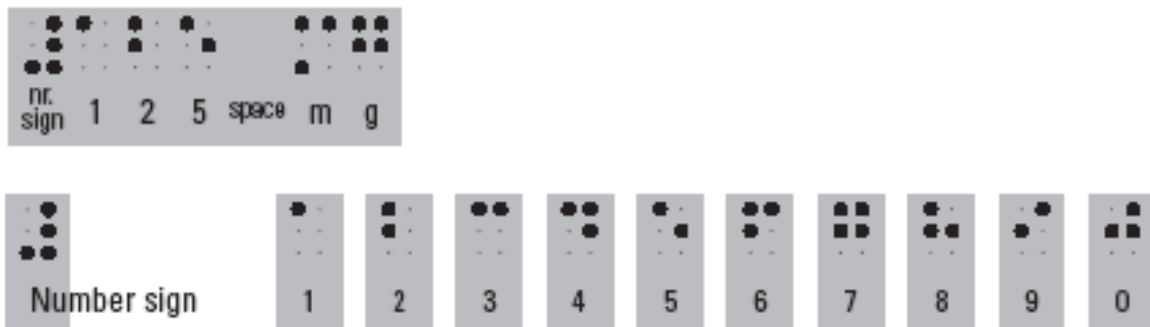
Transitional periods for implementation of Braille labelling on medicinal products which are already subject of a marketing authorisation vary for the different European countries and are detailed in *Appendix 1* as far as regulations have already been published as binding.

2.4.1.1 Translation in Braille

Preparing the mandatory Braille labelling on the packaging materials requires a number of additional steps as well as revision of the existing system in the internal workflows of a pharmaceutical company for issuing and updating labelling specifications for the various secondary packaging materials and folding cartons used. One of the vitally important steps is the generation of reliable translations of the names of all pharmaceutical preparations of a marketing authorisation holder in Braille. In fact, there is a number of Braille converters easily accessible via the internet (e.g. Braille-Converter of Christoffel Blindenmission [16] or Translatum [17]), however, these converters usually lack an adequate certificate ensuring the validity of the translations. Therefore, it has been proven reasonable to make use of the services of official institutions for blind and partially-sighted persons, such as the “Deutsche Blindenstudienanstalt e.V.” (Blista [18]) for generating reliable translations. These institutions do not only ensure a reliable translation of the names of the medicinal products but also take into account specific regulations for Braille writing, such as the correct translation of numbers (i.e. the particular number sign is followed by the letters A to J for indicating the numbers 1 to 0, the number is always terminated with a space; see *Figure 2-4*).

Syllable division in Braille, however, is done in the same way as it is the case for black print, i.e. the scripture used by seeing people. The additional punctuation mark for “-” is added as Braille text.

Figure 2-4: International standardisation of number; number sign [19]



2.4.1.2 Nationally different special characters in Braille for European languages

When translating the name of the respective pharmaceutical preparation in Braille, the nationally different special characters in Braille for European languages have to be considered for products marketed within different European member states. This has to be taken into account especially for those preparations, where the name of the preparation differs for the various European languages and specific national characters form part of the name. However, these different characters have to be considered also for peculiars, such as “/” or “%”, which are translated differently in Braille in some European languages (see *Figure 2-5*).

Consequently, even for preparations authorised according to the centralised procedure (CP), which implies one common name for all European member states (see Title II, Article 6, subsection 1 of Regulation No. 726/2004 [20], different national Braille translations may be necessary.

Therefore, close cooperation with the different national associations of the blind in the various European member states is highly recommended for correct and reliable translations. This is especially true as at least for the German pharmaceutical market, a number of recalls for pharmaceutical preparations has already been published in the specialised press (such as *Deutsche Apotheker Zeitung, DAZ*) due to mistakes in the Braille labelling.

Figure 2-5: Examples of nationally different special characters used in six EU languages (as per September 2005) [19]

Examples of nationally different special characters used in six EU languages

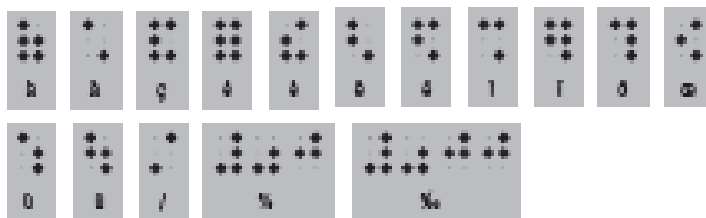
English



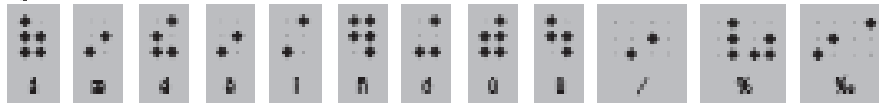
German



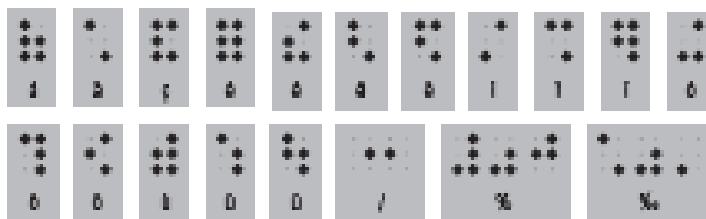
French



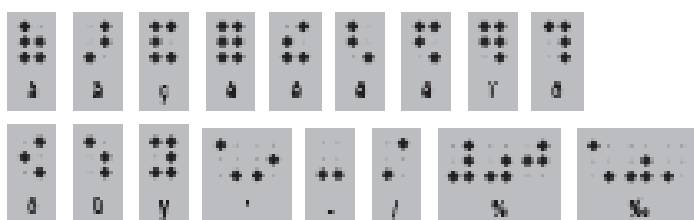
Spanish



Italian



Dutch



2.4.1.3 Braille labelling for multilingual packaging

The “Guidance concerning the Braille requirements for labelling and the package leaflet (Article 56a of Directive 2001/83/EC as amended)” [2] requires that in case of multilingual packaging, the name in Braille has to be printed in all different languages concerned.

Whereas the Braille labelling as far as national specific characters are considered, puts an additional burden on pharmaceutical manufacturers due to the diversity of different organisations of blind to be dealt with to ensure adequate and reliable national translations, Braille labelling is often rather impossible in case of multilingual packaging. Especially for medicinal products manufactured in small quantities only, production of multilingual packaging is of benefit to reduce production costs and to ensure the availability of these products for a wide range of markets and countries. Countries like Belgium require multilingual packaging per se due to the different national languages in the country itself. Implementing Braille labelling for different national translations of the product name on the outer packaging will be limited due to the size of the folding carton, especially since the names of pharmaceutical preparations have consistently grown in the past to increase the safe use of medicinal products (details on strength, on patient groups etc.). As the size of the outer packaging cannot be increased extensively without disregarding legal regulations (see also section 2.3.1 *Status of implementation of Braille labelling in Germany*), these new regulatory implications may decrease the number of multilingual packagings where these are not manageable with regard to multilingual Braille labelling and split in different mononational packaging is required. Worst outcome would in fact be concisions and restrictions to the availability of medicinal products due to an inadequate commercial ratio of expenses and sales.

As any restrictions to the availability of medicinal products as detailed above should not be considered adequate compared to the requirements for Braille labelling taking into account each national peculiarity, facilitations should be implemented on a European level to ensure acceptance of all European member states. One solution could be the inclusion of Braille labelling for the actual trade name of the product combined with the requirement to deliver the national Braille labelling on separate information sheets or adhesive labels in case of dispensing the product to blind or partially-sighted patients in a pharmacy, i.e. just the way Germany handles the necessities for manufacturers of homoeopathic medicinal products etc. (see section 2.3.1.2 *Facilitations according to German Drug Law*). It could also be thought of printing a phone number of a helpline (exempt from charges) of the pharmaceutical manufacturer in Braille on the outer packaging where the respective patient may request a complete Braille label to be sent to his home address. Thirdly, the implementation of a commonly accepted abbreviation system on a European level for frequently used expressions as part of names of

pharmaceutical products, the use of contracted Braille system or of Small English Labelling as an exception would be of help.

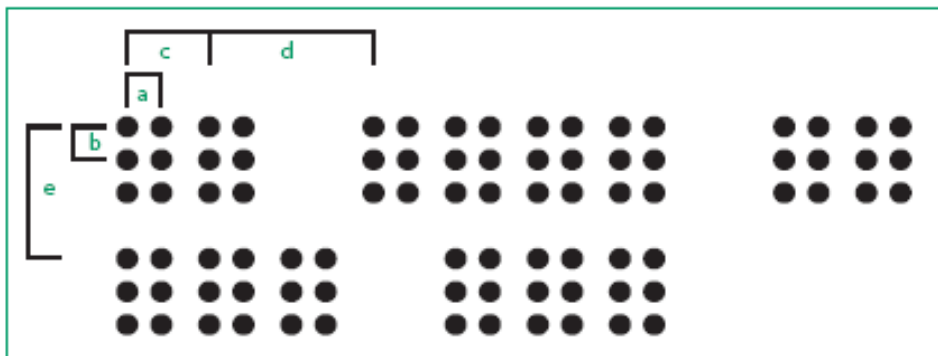
2.4.1.4 Requirements for Braille on folding cartons (technical aspects)

According to the draft standard DIN 55561 “Packaging – Braille on Labelling”, published in June 2006 [13], a standardisation for the manufacture of Braille on labelling cartons in Germany, the following recommendations of the German Study institute for the Blind in Marburg (Blista) are applied:

- Use of full scripture (i.e. uncontracted system)
- Dot-/character dimension “Marburg Medium” is used
- Dot diameter: 1.6 mm (basic diameter) = diameter on the female matrix and on the artwork film / artwork file
- Dot distance: 2.5 mm (from dot centre to dot centre)
- Character spacing: 6.0 mm (from dot centre to dot centre)
- Line spacing: 9.9 mm or 10.0 mm (see *Figure 2-6*).

Figure 2-6: Dot distances (Marburg Medium) according to recommendations of the Germany Study institute for the Blind in Marburg [13]

Dot matrix



Dimensions:

a = 2.5 mm

b = 2.5 mm

c = 6.0 mm between two letters of one word

d = 12.0 mm hyphenation

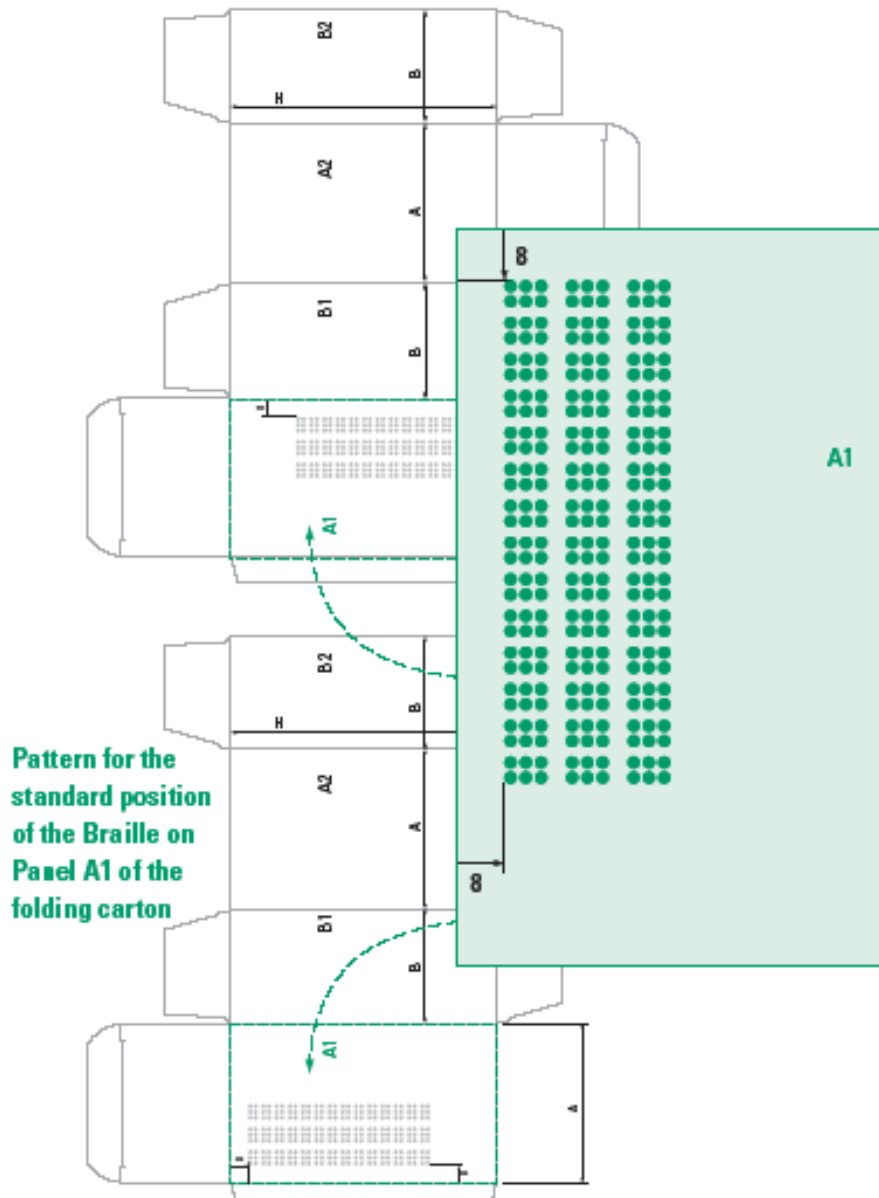
e = 10.0 mm +0.0 mm /-0.1 mm line spacing

For embossing the Braille labelling separate cutting and creasing tools have to be produced, which should preferably be used for all folding cartons of one dimension to reduce costs, i.e. Braille should be placed on a universal matrix on only one main side of the folding carton (e.g. A1). The product-specific male part of the embossing system is then used for the actual Braille labelling. The distance between the place for embossing and the middle of the cutting and creasing lines has to be 8 mm (from the end of the dot) (see *Figure 2-7*) [11]. It has to be ensured that the Braille labelling is not located on places where labels / Bollini, barcodes (EAN / PZN) and perforations are applied on the folding carton; the Braille labelling, however, is not required to be placed on a blank, white subfont.

Manufacture of Braille on (adhesive) labels may also be performed by screenprint, which ensures that the Braille-dots are well-palpable and also long-lasting, i.e. not damageable due to mechanical exposures during transport. The height of the Braille-dots should be at least 0.12 mm to be well-palpable, however, the legibility and optical characteristics should not be impaired for seeing people due to a potentially broken and / or bursting surface of the folding carton [21].

Both, after embossing or screenprinting of Braille-dots, they will undergo a slight back-formation due to mechanical and climatic factors.

Figure 2-7: Positioning of Braille on folding cartons



2.4.2 Implications on the outer packaging materials, manufacture and release procedures

2.4.2.1 Description of necessary internal steps for creation of Braille labelling on folding cartons and proposal for a workflow within pharmaceutical companies

Implementation of the requirements of Braille labelling for the portfolio of a marketing authorisation holder according to Article 56a of Directive 2001/83/EC [1], as amended, and the respective Guidance concerning the Braille requirements for labelling and the package leaflet, dated 2005, [2] demands a detailed listing of all pharmaceutical products currently marketed and actually being affected by the provisions of the above mentioned standards. The tabulation should detail any transition provisions and any particular specifications per member state including the dates where Braille labelling is obligatory. Concerning particular requirements per member state, the United Kingdom may serve as an example as Braille is also needed to be applied to containers which are not subsequently enclosed in an outer carton, e.g. bottles [22, Question 11]. Furthermore, national transposition of the European standards in the United Kingdom goes beyond what is detailed in the Guidance concerning the Braille requirements for labelling and the package leaflet, dated 2005, [2], as they ask for alternative means of providing Braille information also for small volume packages up to 10 ml (e.g. use of contracted Braille system or certain defined abbreviations or addition of supplementary “tab” label) [22, Question 15].

This listing, usually to be issued by the regulatory affairs manager with support of marketing colleagues, should include the complete names of the preparations under which they are marketed within the European member states, if different. These names will afterwards be translated into Braille, taking into account specific national differences in terms of characters as well as legal requirements (see *Appendix 1*). These translations may be done by help of the print offices used for printing package leaflets and folding cartons or by involving the respective national institutions of blind people, such as the Blista in Germany.

Having available the different Braille translations, it is important to work out an optimal plan for issuing the Braille labelled folding cartons. The size of the different folding cartons used has to be regarded including the fact that Braille labelling should preferably be placed on one main side of the carton only. In a number of cases, however, one side of the carton will not be sufficient due to the considerable length of names of pharmaceutical products, which are often required to ensure the safe use and distinction from other preparations. In these cases, implementation of the Braille labelling on two opposite sides of the folding cartons, i.e. A1 and A2 (see *Figure 2-7*), is usually less expensive than using two consecutive sides without interfering with the legibility by blind

people. Furthermore, syllable division has to be adjusted reasonably in case of lengthy names.

In addition, it is worth while to review the complete set of folding cartons used and to utilise the possibility of harmonising at least some of the different carton sizes. This helps to reduce costs when preparing the required cutting and creasing tools for the Braille labelling (see section 2.4.1.4 *Requirements for Braille on folding cartons (technical aspects)*).

These tasks should be coordinated by the regulatory affairs manager, however, they require close cooperation with the department responsible for packaging design.

The next step will be the implementation of Braille in the artwork files by the print office and the final print approval according to the internal release procedures of the pharmaceutical company (see below). The Braille labelling has to be laid down as an additional layer in the artwork file. The colour used to represent the Braille text must not be used for any other written or printed information on the packaging. The Braille in the artwork file, in the print approval file, in the cutting and creasing tool and in the finished folding carton must match exactly. The Braille message must also be reproduced in regular type outside the line of the embossing die.

In order to ensure that the Braille text can be checked at all stages of production, approved proofs for folding cartons carrying Braille must be set up as follows: The first proof page must contain the printed image only and should be used for approving the regular print (see *Figure 2-8*). The second proof page must contain the Braille dots only together with the die-line and the Braille message in alphanumeric text (outside the die-line) (see *Figure 2-9*) [11, 19].

Figure 2-8: Print approval page 1

Print approval page 1

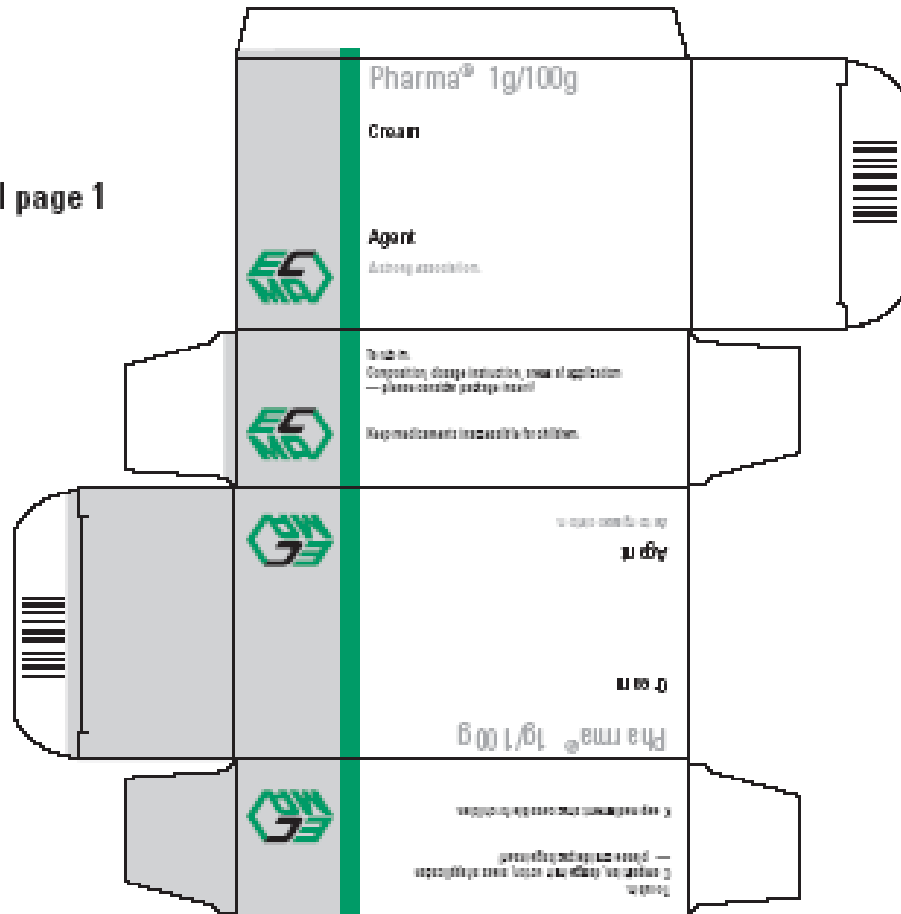
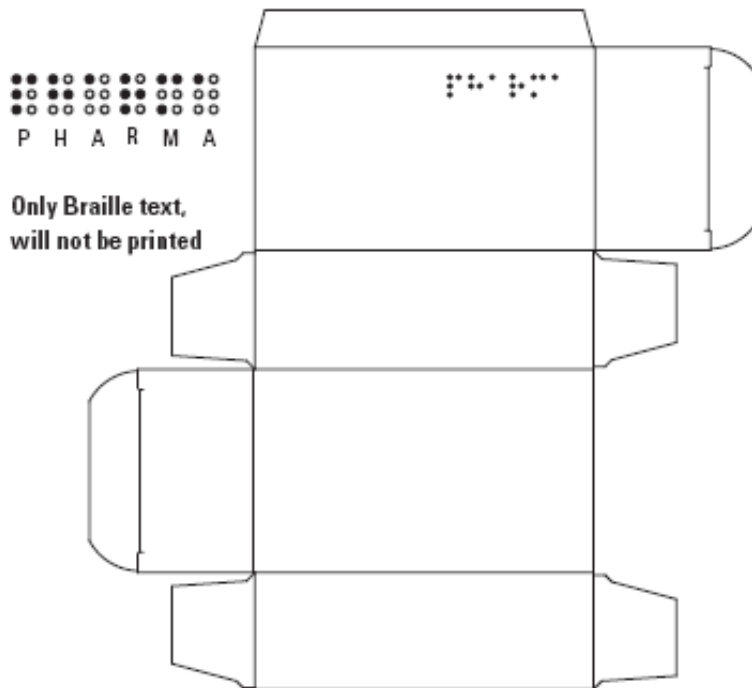


Figure 2-9: Print approval page 2

Braille approval page 2



Approval of these artwork files can be arranged according to the regular internal release procedures within the company, i.e. including the departments usually involved such as drug safety, marketing, regulatory affairs, medical sciences, the respective departments of affiliates or partners in the different European countries and – concerning labelling used for the German market – the information officer according to § 74a, AMG. In order to ensure proper issue of Braille, however, it is recommended in any case to involve the respective national institutions of blind people, such as the Blista in Germany, for review and approval. These institutions are able to guarantee the correct translation in Braille considering national specific characters as well as particular requirements such as “Code Antoine” in France or Belgium. An official certificate of the accurate transformation in Braille can be requested and may be helpful for documentation purposes internally as well as for authority demands. Involvement of these national institutions is especially important in case the first translation step has been done by the pharmaceutical company or the print offices for the folding cartons.

Having implemented the conversion of all affected folding cartons including a revision of the internal workflow addressing the additional needs for implementing and checking the Braille labelling, it has to be ensured that for all future changes in the name of the

pharmaceutical preparations or any additional European member states, where marketing of the products shall take place, the same procedures are adhered to.

2.4.2.2 Implications for internal release of Braille-labelled folding cartons

In addition, internal workflows in pharmaceutical companies have to be revised concerning the quality control and release of incoming folding cartons with Braille. Apart from the traditional checks of imprints by direct comparison with test films, there is a number of different systems commercially available to ensure the correct transposition of Braille on the folding carton. They allow folding carton makers / print offices and the pharmaceutical manufacturers an automated check of the correctness of the Braille imprinting.

Since more than five years test systems for printed packaging materials are commercially available, which allow digital control of these packaging materials and often include the additional possibility of checking Braille. In general, two systems can be differentiated: the “text control”, which matches the textual contents of the master vs. the print and the “chart control”, which matches the print quality also, e.g. logos, figures etc. In all cases the packaging material to be tested is scanned and checked against the master pdf-file. Any deviations are marked on the screen of the computer and an appropriate print-out can be generated to be archived as part of the quality management system within the pharmaceutical company. Examples for such systems are “Braille Compare” by Ladegast Pharma Packaging, “Text Verification Tool” by Schlafender Hase or DotScan by In-Situ [23, 24].

Apart from adequate working procedures for the employees working with these electronic systems and the related training sessions needed, the systems themselves need to be validated, which may be performed entirely or partly by the software suppliers. In any case, implementation and updating of these systems ties up additional costs as well as manpower, albeit the very helpful tool for ensuring a level of quality and certainty for printed packaging materials.

As a matter of course, any technical and quality agreements of pharmaceutical companies with folding carton makers / print offices have to be revised to include the increased demands with regard to Braille on secondary packaging [11].

2.4.2.3 Implications on regulatory activities for Braille labelling

Information on Braille labelling of the outer packaging should be addressed in Module 1, section 1.3.6 “Braille” of the Common Technical Document (CTD). In addition, the information that will appear in Braille on the printed outer packaging should be mentioned, if applicable, as normal text in section 16 of the outer packaging labelling of the respective QRD-templates.

This is in line with the current procedure as implemented at the German BfArM, i.e. indication of Braille labelling in normal text in the labelling designs is sufficient [25].

For marketing authorisations in the centralised procedure, Braille labelling should be indicated with dots on the mock-ups (see Module 1, section 1.3.2 “Mock-up” of the CTD) [26].

By help of indication of the Braille dots on the mock-ups the assessors of the competent authorities are able to check that the actual Braille text applied accurately reflects what is required and that the placement of the Braille text does not adversely affect the readability of the remaining statutory labelling requirements. The British competent authority, MHRA, clearly depicts that there is no necessity to provide touch-readable actual packaging [27].

Although the German Drug Law (§ 11 (1a)) requires marketing authorisation holders to present a specimen of the patient leaflet and of any changed version thereof, the German BfArM usually does not demand the marketing authorisation holders to make available specimen of the patient leaflets. Therefore it remains unclear how supervision of the correct implementation of Braille on the outer packaging will be performed in Germany. It is rather conceivable that the monitoring of the Braille labelling may be part of the routine inspections of the Federal State authorities when checking GMP- and regulatory compliance and testing selected medicinal products for their pharmaceutical quality and conformity to specifications.

The Irish Medicines Board (IMB) even goes one step further and clearly details in an announcement that they require marketing authorisation holders to provide a “declaration of compliance” with new applications or variations to update patient informations that these are in line with the provisions of Article 56a of the new European Medicines legislation. A master declaration is provided. The Market Compliance Section of the IMB Compliance Department will then check compliance of the labelling and the other provisions of Article 56a. As part of this work, the Market Compliance Section will obtain samples of relevant medicinal products from the marketplace for checking, and will also perform inspections, as necessary, in order to monitor compliance with the provisions of Article 56a and with the declaration provided [28].

Implementation of Braille does not require a separate variation to the marketing authorisation but competent authorities encourage marketing authorisation holders to include other regulatory changes in addition to adding Braille to the packaging. In fact, this can be judged as a concession of the competent authorities to avoid additional bureaucratic burdens including additional costs for the huge number of variations that would be needed.

2.5 Package information leaflets in formats appropriate for the blind and partially-sighted

It has been complained already ten years ago that the package leaflets accompanying pharmaceutical preparations leave patients with impaired vision behind. This has been especially alarming as most visually impaired people are elderly ones, a group that is prescribed a good portion of all prescription drugs and, in addition, often also uses a number of different drugs at the same time [29]. In addition, the proportion of elderly people in the visually impaired population is on the increase. They are a key target group due to their special vulnerability. The British Royal National Institute for the Blind's "See it Right" campaign pointed out that visually impaired people have a right to equal access to information, including medical information. It was, however, also underlined that blind and partially-sighted people are not a homogeneous group, but are of all ages and backgrounds, making it necessary to provide the package leaflet as different means.

The request of blind and partially-sighted patients for self-determined information on medicinal products, regardless whether prescription drugs or over-the-counter medicines, and the need for adequate formats of the package leaflets has been addressed as part of the latest revision of the European Drug Law. The legal text of Directive 2001/83/EC, as amended by Directive 2004/27/EC, Article 56a is as follows: "*...The marketing authorisation holder shall ensure that the package information leaflet is made available on request from patients' organisations in formats appropriate for the blind and partially-sighted.*" (see section 2.1 *Regulatory background*) [1]. The respective national transposition in the German Drug Law has been at hand with the 14th amendment of the AMG, dated 29.08.2005, § 11 (3c) AMG [7].

It is helpful that the European Directive does not detail the means and formats that are deemed applicable to serve the needs of blind and partially-sighted patients in this respect. The same applies for almost all European member states with regard to the national transposition of this requirement (see *Appendix 1*).

Interestingly enough there are no transposition periods foreseen so that the requirements of Article 56a directly apply according to the implementation dates of the

national drug laws. The German Federal Ministry of Health, however, specified that the request from patients' organisations for these particular package leaflets requires an adequate coordination between the associations of the blind and partially-sighted people and the associations representing the marketing authorisation holders. As this discussion between both parties has already been started, the legal requisites are met and the execution period of this requirement according to § 11 (3c) AMG has begun [30], i.e. the legal requirements in Germany are met by the pharmaceutical industry.

2.5.1 Potential approaches for implementation in the pharmaceutical industry

Providing the package leaflets of all pharmaceutical products marketed within the European member states in formats appropriate for blind and partially-sighted patients is rather challenging for pharmaceutical companies due to the fact that the needs of these patient groups are fairly diverse so that a number of various systems will have to be implemented to actually meet the needs of these patients.

This shall be demonstrated by two examples: Making available the package leaflets in large font sizes, e.g. font size of 18 or 20 pt⁵, will not be adequate to serve blind patients or patients with general reading difficulties [31]. Producing the package leaflets as audio books on CD-Rom would be of help, however, this approach will be a very cost-intensive and time-consuming one as the contents of package leaflets are subject to numerous changes, which requires an automated, digital conversion of the files to audio formats⁶ and, on the other hand, it cannot be taken for granted that especially older patients have access to a suitable CD-Rom player. This applies especially with regard to the possibility of placing the package leaflets on the websites of the pharmaceutical companies as these are not easily accessible especially by older patients or patients with less pronounced skills.

As the respective EU-Directive requires these package leaflets on request of patients' organisations only, the marketing authorisation holder is not obliged to maintain suitable formats of the package leaflet. The request of a said organisation rather specifies the legal requirement so that an adequate time period has to remain for the pharmaceutical company to provide the package leaflet. Otherwise the necessity of implementing the request of patients' organisations in the Directive would not have been reasonable.

⁵ Enlarged print is 14 pt or 16 pt or regular print that has been enlarged using magnification devices. Large print is 18 pt type and larger. Enlarged print and large print are accommodations.

⁶ Publishing package leaflets in audio format by using narrators requires experienced narrators with appropriate voice, speech, accuracy and pronunciation skills. Using this approach for package leaflets will surely turn out to be an expensive one due to the high frequency of changes of the package leaflets.

Despite of this the marketing authorisation holder has to implement suitable systems for accomplishing these requests within a reasonable time frame. For that purpose it is assessed to be very helpful that a couple of European member states have implemented national centralised systems for making the patient information leaflets available, e.g. as part of a common pharmaceutical compendium database (e.g. Denmark, Finland, Norway). For most member states audio formats of the leaflets are the preferred options (see *Appendix 1*).

2.5.1.1 Implementation in Germany: The RLS-Project

For Germany it is planned to implement a patient information service as a completely new information and communication tool for package leaflets; it will be available at <http://www.patienteninfo-service.de>. This project is currently dealt with by the Rote Liste® Service GmbH (RLS) in close cooperation with representatives of the German pharmaceutical associations BPI, BAH and VFA. The work in this group is carried out in close collaboration with the German “Deutscher Blinden- und Sehbehindertenverband e.V.” (DBSV) and the German “Deutsche Zentralbibliothek für Blinde” (DZB).

This task force has been established to avoid cost-intensive separate local solutions at the various pharmaceutical companies, including adaptations at short term to implement the required electronic systems and documents, and aims at offering various data formats based on XML-files from a central platform. This is due to the fact that the currently available systems of the RLS, “ROTE LISTE® Online” and “FachInfoServiceOnline”, i.e. compendia detailing relevant information about pharmaceutical preparations and the German summary of product characteristics (Fachinformation, FI), respectively, already offer pharmaceutical information on a neutral basis for almost ten years. Consequently, it appeared reasonable to widen the services and offer access to patients also due to the increasing interests and demands of the public regarding health topics [32].

The services of this intended “PatientenInfo-Service” will comprise the following:

- Supply of current versions of patient information leaflets for patients as well as medical / pharmaceutical circles (experts)
- Current versions of the patient information leaflets are provided by the pharmaceutical companies to the public as neutral information
- Patient information leaflets will be made available to blind and partially-sighted patients via internet
- XML-based and standardised patient information leaflets for future electronic exchange between the pharmaceutical companies and the competent authorities.

In cooperation with the DBSV the above mentioned task force worked out the following formats to be suitable for package leaflets for the purposes of the blind and partially-sighted patients in Germany to meet the requirements of the European Directive and the German Drug Law respectively:

- Customised websites of the package leaflets for inquiry and edition with assisting techniques such as ScreenReader, Braille etc.
- Taped package leaflets on data media such as audio-CDs and via internet
- Package leaflets in large font sizes
- Braille print.

The favoured options are the audio formats, if possible processed with the so-called DAISY-format, which allows navigation in the audiodata also. By using DAISY (Digital Accessible Information System), a talking book format is presented that enables navigation within a sequential and hierarchical structure consisting of (marked-up) text synchronised with audio. For this reason, DAISY books are superior to regular audio books due to the possibility of navigating the content and displaying synchronised text. They can enable blind users to navigate an encyclopaedia and, consequently, the DAISY system would also permit blind patients to easily navigate patient information leaflets without external help [33, 34].

2.5.1.1.1 Technical aspects of the RLS-project

The technical system behind the planned RLS-project will be an XML-structure, based on an RLS-standard data DTD (Document Type Definition). This RLS-standard-DTD may be created based on word-/rtf-files of the package leaflets according to the QRD-templates or the requirements for package leaflets according to the 14th amendment of the German Drug Law. Further possible file formats to be converted to RLS-standard-DTD are XML-files based on PIM-structure⁷ (Product Information Management) [35], company-defined DTDs or the RLS-standard-DTD.

Starting with the RLS-standard-DTD a number of different output formats is feasible: print versions such as large font layout, Braille-print, audio versions such as MP3-files and DAISY-format and finally electronic media such as XHTML websites.

The system by RLS as being presented will be a major step forward for the pharmaceutical companies participating in this project as it will give the opportunity to create XML-based product information documents, which can be converted to the various output formats as detailed above and, even more important, enables to exchange the documents via the PIM-project with the EMEA and with the national competent authorities once the PIM-system is implemented not only for the centralised procedure. These XML-based product information documents are advantageous especially with regard to the number of necessary changes and adaptations for the summary of product characteristics (SmPC) and all related product information texts. XML-based documents can be easily fragmented in different sections, which can be adapted and revised separately. This is of big advantage as these sections may be used repeatedly throughout one document and different documents also, e.g. in case of revising the information texts of one pharmaceutical product presented in different strengths. As a matter of fact, using these text modules helps to gain time, but more importantly, it is a tool to decrease the number of failures and shortcomings in the

⁷ Primarily PIM is a standard for the electronic exchange of product information (summary of product characteristics, package leaflet and labelling) in the context of marketing authorisation applications. It describes how the required information should be created and validated so that it can be exchanged successfully between applicants and competent authorities. The design of the standard aims to minimise the repeated adjustment of information that is included many times in different locations within the documents provided in support of current processes. Its guiding design principle is to hold any piece of information only once and to allow its use as many times as necessary to create the required documents. It will obviate the need to supply either paper or Microsoft Word documents, as are currently required. The standard utilises XML to structure and control the product information being exchanged. Product information documents for a product are split into pieces, labelled and put into a database. Identical pieces are kept once.

The standard has been developed to support products submitted for evaluation via the centralised procedure only in the first instance. The scientific content and layout of required documents is defined to be compliant with the Quality Review of Documents (QRD) templates.

It is anticipated that once the use of PIM is embedded within the centralised procedure the standard will be further developed to support products in the mutual recognition, decentralised and national procedures.

process of creating product information texts and exchanging them with the competent authorities.

Consequently, the RLS-project is of high value as it offers pharmaceutical companies the possibility to participate in a comprehensive venture, encompassing a variety of options, i.e. presentation of package leaflets in formats suitable for blind and partially-sighted patients, conversion of the XML-files according to the RLS-standards in company-specific layouts for presentation of package leaflets and preparation of XML-files as a prerequisite for participating in the PIM-project as outlined above. It is also advantageous that the quality of the derived presentations will be the same for all pharmaceutical companies joining the RLS project, i.e. retrieval of information will be facilitated for the patients using the "PatientenInfo-Service" platform.

The RLS-project, however, requires the product information texts to be written according to the updated QRD-templates and the requirements of the 14th amendment of the German Drug Law, respectively. As not all companies have managed to rewrite the texts for all the pharmaceutical preparations marketed by now, the RLS will offer an interim solution. Those package leaflets not yet transformed according to the latest requirements will be provided by the RLS as pdf-files and may be used by patients in a restricted way, i.e. magnification will be possible as well as conversion to Braille and to spoken language.

In future times, the RLS-project even plans to widen the range of products to be offered such as incorporation of foreign-language package leaflets, sending of printed package leaflets via post or fax-message following a telephone request or customer services like preparation of (large) prints.

2.5.1.1.2 Responsibilities according to the German Drug Law with respect to the RLS-project and legal aspects

Nevertheless, there are some facts that need to be considered carefully to ensure the reliability of the data generated by the new RLS initiative.

Transfer of data from the pharmaceutical companies to the RLS for conversion into the RLS-standard-DTD should be performed electronically using a safe and protected internet gate, accessible by passwords only. Of course, the same should apply to future exchange of any adaptations of the product information texts, e.g. after having approved a variation by the competent authorities. It would be appreciated if the communication and exchange of data between the pharmaceutical companies and the RLS, and vice versa, is not a monodirectional communication as currently applied for the Rote Liste[®] Compendium in Germany, but is a database with demanding access restrictions where

both, pharmaceutical companies and RLS, are able to work on the same files. This is considered extremely helpful for the check for correctness and final release of the converted files by the pharmaceutical companies, particularly in terms of the duties and responsibilities of the information officer according to § 74a of the German Drug Law. The information officer is responsible for ensuring compliance with the prohibition to prevent deception (§ 8 AMG) and ensuring that the labelling, the package leaflets, the professional information and advertisements correspond with the content of the marketing authorisation or registration. Consequently, implementation of an easily but safely accessible information platform for the RLS-project is deemed vitally important. In order to be acceptable for data transfer and data processing of product information documents, the software used for the RLS-project needs to be fully validated in terms of computer and database validation including an adequate documentation of the validation.

Apart from the responsibilities of the information officer it has to be discussed also whether the generation of different output versions of package leaflets and the exchange of these output versions with patients' organisations by the RLS has to be considered as part of the manufacturing process of a pharmaceutical preparation and therefore requires a manufacturing authorisation according to § 13, German Drug Law (AMG). § 2 (14) AMG details manufacturing as "the producing, preparing, formulating, treating or processing, filling as well as decanting, packaging, labelling and release of medicinal products". As the European Directive 2001/83/EC, as amended, details in Article 56a that the package information leaflet has to be made available on request from patients' organisations in formats appropriate for the blind and partially-sighted patients – which has been transformed almost literally in the German Drug Law – it can be deduced that the intention of the European Directive is not to characterise the range of products offered by the RLS as a manufacturing step in the sense of "packaging" and also not as a promotional tool by the different pharmaceutical manufacturers. This understanding would be in line with a court decision concerning the Law concerning Advertising in the Health Care System (HWG) of the Higher Regional Court Munich, dated 07.03.2002, according to which the accessibility of summary of product characteristics without particular DocCheck-Requirements is not judged as unallowed advertising as long as the SmPCs are available only in case the search for the SmPC is based on a particular interest on the respective pharmaceutical preparation [36]. In line with this decision, the Higher Regional Court Munich decided in 2004 that the accessibility of a package leaflet for a prescription-only medicinal product in the internet is allowed as long as the patient searches for this information by purpose [37].

A further item that should ideally be standardised for all companies joining the RLS-project is the description of drawings, pictures etc. which may form part of the product information texts, e.g. illustrated instruction for preparation and application of a certain dosage form. As these items can not be text-coded and therefore can not be directly transformed into different output options, additional text descriptions need to be supplied, which should ideally be similar for the different possible situations throughout the pharmaceutical industry.

Finally, it should also be ensured that confusion of patients and / or their relatives and caregivers using the future services of the RLS-project is avoided due to the fact that the contents of the package leaflets are subject to numerous and frequent changes. Appropriate information, detailing that the most up to date version of the package leaflet of each pharmaceutical preparation is available on the "PatientenInfoService"-page only, would be appreciated, clarifying that the medicinal product bought in a pharmacy might be equipped with the previous edition of the package leaflet without any negative influence on the information status of the patient.

2.5.1.1.3 Potential shortcomings of the RLS-project

It seems that the services of the RLS might not be suitable for each pharmaceutical company despite of the comprehensive facilities of the newly to be implemented RLS-project in terms of serving the needs of blind and partially-sighted patients in particular and also for each patient being interested in having access to the most up to date version of the package leaflet of his medication. Taking into account the need to continuously exchange and update the information on package leaflets between the marketing authorisation holder and the RLS, the need to ensure the correctness of the conversion into the RLS-standard-DTD files etc., the personnel expenditures for these tasks in addition to the fees to be paid to the RLS might not justify participation in the RLS-project for a number of very small or medium-sized enterprises (SME), especially when they are concentrating on a small range of products that are produced in small quantities only.

For these companies it might be more appropriate to e.g. provide telephone services on free numbers in the package leaflets and install a hotline / call center being able to read the package leaflet for all or only selected parts, to repeat certain sections and answer questions if required. The latter would in fact be more reasonable for those groups of patients for whom leaflets may present problems, e.g. people with reading difficulties.

Considering Braille labelling of all pharmaceutical preparations, the situation was greatly facilitated for marketing authorisation holders with implementation of certain transition periods and exceptions (see section 2.3 *Status of implementation at European member*

state level and section 2.3.1.2 *Facilitations according to German Drug Law*). Only by help of implementation of these exemptions, e.g. (Braille – miget amounts – regulation, dated 14.07.2006 [12]), the variability of medicinal products on the market can be maintained. Otherwise it was anticipated that a number of products, e.g. homoeopathic medicinal products, would have no longer been manufactured without tremendously increasing prices, a circumstance that would have been unacceptable for the patients.

As a consequence, it is suggested to implement certain exceptions with regard to the availability of package leaflets in formats appropriate for blind and partially-sighted patients also, e.g. by accepting a service hotline, free of charge, as outlined above. In addition, it would be worth thinking about facilitating these additional burdens especially for small and medium-sized enterprises and pharmaceutical companies manufacturing only a small number of medicinal products in marginal amounts. Alleviations would surely also be conceivable for medicinal products used by healthcare professionals only, at least for those which are used at intensive care units only in contrast to e.g. vaccines or comparable preparations. Again, any exceptions are of help for pharmaceutical companies only, if a common approach could be reached by all European member states.

2.5.1.2 Guidelines from the European Blind Union (EBU) and implementation in the United Kingdom (UK), the Netherlands and Sweden

The European Blind Union (EBU) which represents more than 10 million blind and partially-sighted consumers in Europe has issued guidelines regarding the implementation of package leaflets accessible for visually impaired end-users [15]. In any case, they request that the choice of the appropriate medium should be made by the marketing authorisation holder in close consultation with representatives of organisations for the blind and partially-sighted. The EBU has set up a list of requirements, which should as a minimum be met to address the needs of the respective patients. These are the following:

1. To ensure that all visually impaired end-users of medicinal products are accommodated, package leaflet information must be made accessible in all relevant formats, i.e. in the three main formats: Audio, large print and Braille.
2. All package leaflet information must be made available free of charge to visually impaired end-users regardless of format.
3. The system / systems applied must be modular, i.e. flexible and available for upgrades.

4. Any national system must offer the information in the relevant national language / languages. If a system is meant for service in more countries / language zones, it must be adaptable for all relevant languages.
5. It must be applicable in all relevant technical environments. Thus, if services are rendered via the telephone and / or the internet, the systems used must accommodate the end-users' specific needs and possibilities regarding ability to access information. The information must be made readily available, i.e. in a timely manner and without delay.
6. To make the system as transparent as possible for the visually impaired end-user, all possible efforts should be made to ensure that a single point of contact nationally or even regionally is established. This will help to avoid confusion as to where to go to order package leaflet information and also be the best way to avoid duplication of the same information. This principle of information retrieval from a single point should not limit the possibility of sub-contracting production to private or public entities with the necessary expertise and equipment.

Taking these requirements of the EBU into account, the final implementation of the RLS-project in Germany will address all these issues once being set alive.

In the following, the implementation of the European Directive of making available the patient leaflets in formats appropriate for blind and partially-sighted patients as performed in the United Kingdom, the Netherlands and Sweden is examined also.

In the United Kingdom a comparable system as the German RLS-project has already been implemented. It is a combined solution of some industry trade associations including a provider for the electronic system and the national blind associations, the so-called "X-PIL", which was launched beginning of November 2006 [38]. X-PIL ensures that patient information leaflets supplied with medicines are accessible to everyone, including those with sight problems. It is a leading source of reliable and up-to-date information on UK medicines. The web site is managed by Datapharm Communications Limited. All package leaflets on the web site are supplied and updated regularly by UK pharmaceutical companies. They can be viewed in different sizes on the screen by clicking on the font size-menu. In addition, the website details a single national phone number (free to use and operating day and night) of the Royal National Institute of the Blind (RNIB), where the leaflets can also be requested in audio, Braille or large prints. This free service is supported / promoted by pharmacists and the NHS.

Navigation of the well arranged website is quite simple and self-explanatory. The search may be easily performed by either "Browse leaflets" or "Browse companies", for each being arranged in alphabetical order. Having chosen a particular leaflet of interest, the website again offers different options for presentation of the package leaflet. In case of

questions, a very comprehensive and well-structured help page including “frequently asked questions” is available. Although the web site has not yet been completely established with all package leaflets available, it is judged as a very comfortable and attractive tool for patients – even for those not regularly dealing with web sites. In fact, it would be highly appreciated if the German RLS-project will be as clear and concise once being established to ensure its acceptance and usability by the majority of patients.

The Netherlands implemented a National Package Leaflet Telephone Line where blind or visually impaired consumers can ask to listen to the text of a package leaflet or obtain it in another format (Braille or large letter). The project is conducted by the Confederation for the Interests of the Visually Impaired and the Blind [39]. This phone line is available from Monday to Friday during working hours and costs appr. 0.03 € / min of local rate. The launch date of this phone line was 05.07.2006. Marketing authorisation holders have to supply the phone line with detailed data concerning their medicinal products.

When calling this line, patients are greeted by an automated voice and are presented a short options menu. In order to listen to the package leaflet text, the patients have to key in the respective marketing authorisation number on their telephone. The most up to date version of the PIL as part of the Medicine Evaluation Board's (CBG – MEB) database is used and is digitally-spoken via a computer or read out by a trained line operator if no digital version is available.

It seems rather questionable whether patients, especially blind and partially-sighted ones, will in fact be able to enter the marketing authorisation number of the respective medicinal product on their telephone – a prerequisite to listen to the package leaflet. Patients will probably more likely remember the name of the medicinal product and will surely have problems in allocating the marketing authorisation number in a package leaflet. Asking the pharmacist to write down the respective number will not be helpful in case of any medication bought outside a pharmacy. In addition, an error in typing in this marketing authorisation number on the telephone could result in extensive confusion of the patient in case the wrong number typed in actually fits with another marketing authorisation number of a different preparation. In any case, an additional check would be preferred after having typed in the marketing authorisation number to affirm the correct name of the medicine. For that reason it is rather understandable, that the National Package Leaflet Line carries a disclaimer of liability that it is not responsible for incorrect use of a medicine.

After having listened to the package leaflet text, the patients may order the text in Braille, large print or as word file. In any case, the request including contact details of

the caller is passed on to a particularly allocated contact person at the marketing authorisation holder.

To conclude it seems that the Dutch system fulfils the requirements of the European Directive, however, it lacks some kind of safeguarding for the patient requesting information on package leaflets as outlined above and, in addition, the marketing authorisation holders do not receive nameable support in handling the needs of these special patient groups. Consequently, this system is not at all comparable to the very sophisticated and comprehensive offerings of the German RLS-project, which is most likely to relieve the pharmaceutical companies once having rewritten all package leaflets according to the current requirements of the QRD-templates.

In Sweden a website was created by the pharmaceutical industry, which discloses electronic versions of all existing patient leaflets [40]. The package leaflets are accessible by entering the name of the pharmaceutical product or the drug substance name. The package leaflets may be easily displayed in different font sizes and may also be read by a synthetic voice. Furthermore, extra information is included for description of the various dosage forms, for further explanations on contraindications etc. In addition, a system has been set up so that companies or the pharmacy (at time of dispensing) can order a leaflet with Braille to be printed out and sent by post to the patient. The whole project is run in cooperation with the patient organisation for the blind and visually impaired.

Although the system misses an encompassing helpline with frequently asked questions as it is available for the British web site, it seems well arranged and easy to navigate and understand. Large print sizes or digital reading of the package leaflet is easily possible as well so that the system implemented in Sweden seems to be suitable to actually serve the needs of blind and visually-impaired patients – provided that blind patients possess the required means to operate a keyboard and navigate in the internet.

2.6 Critical evaluation

2.6.1 Braille labelling

According to the information of the Deutscher Blinden- und Sehbehindertenverband e.V. (DBSV) a number of 155,000 persons in Germany are blind and about 500,000 persons are visually-impaired. In total, about 29,000 of the blind and visually-impaired persons in Germany have a command of the Braille reading and writing [41], i.e. less than 0.5% of the blind and visually-impaired persons. For Europe, the number of blind and partially-sighted persons amounts to appr. 7.4 million compared to a number of appr. 459 million people living in Europe [15, 42].

Although there is no doubt about the plausible request of blind and partially-sighted patients for self-determined information on medicinal products and the need for adequate formats of the package leaflets to ensure equal opportunities, it should not be forgotten that implementation of the respective tools for meeting these requirements involves demanding additional input of the pharmaceutical companies from a financial point of view [9]. It does not include reprint of the outer packaging materials only to implement Braille but implies complete revision and adaptation of all processes and workflows within a pharmaceutical company including the ones with external service providers such as print shops. Furthermore, it means implementation of additional systems and quality checks especially with regard to correct Braille labelling as detailed above. Due to the fact, that the supplemental costs will most likely not result in higher sales prices, it should be highlighted that these efforts represent an exceptional commitment of the pharmaceutical industry.

In any case, it should be avoided that due to these extra costs and activities for implementing Braille labelling on the packaging materials and providing adequate formats of the package leaflets for blind and partially-sighted patients, marketing authorisation holders feel impelled to resign further production and marketing of particular pharmaceutical products due to a pronounced imbalance of the additive costs and work flows. This would surely be a worse outcome for a regulatory initiative, which more than deserves to be supported and fostered but in contrast has not even been subject in the frequent newsletters issued by the Deutscher Blinden- und Sehbehindertenverband e.V. during the last couple of months.

Especially with regard to Braille labelling on outer packaging, it would be highly appreciated if a consensus on European level would be feasible to agree on common requirements and regulations, e.g. with regard to Braille conversion of specific characters in the different European languages (see Figure 2-5). This would be helpful not only for multilingual packagings but would also diminish the number of required cutting and creasing tools and the number of potential errors as well. Apart from that, a European consensus on using Marburg Medium as a commonly accepted Braille labelling system for all European member states as opposed to different national approaches (such as “Code Antoine” in France and Belgium) would facilitate the implementation in the pharmaceutical companies enormously. The same applies to common agreements on a European level with regard to mutual implementation for exceptions of the Braille requirements for small volume packages and a common European “Braille Dictionary” detailing Braille abbreviations for often used expressions to shorten the Braille labelling especially in terms of the increasing length of names of pharmaceutical preparations.

The German draft standard DIN 55561 “Packaging – Braille on Labelling”, published in June 2006 (see section 2.3.1.3 *Marburg Medium for Braille characters*) could serve as an excellent starting point for such a common European approach. It should also be considered to adopt the German “Regulation on labelling of medicinal products with Braille for miget amounts (Braille – miget amounts – regulation, dated 14.07.2006)” [12], detailing exemptions from Braille labelling for medicinal products, which are manufactured in quantities of not more than 7000 packages per year, on a European basis as it is a sound consideration for a compromise between the needs of the blind and partially-sighted patients and the pharmaceutical industry.

Apart from the requirement of Braille labelling of medicinal products, it should be scrutinised whether the range of this requirement would need to be widened to cover further products with potential harms such as washing powders and cleaning agents as well as items such as foodstuff or cosmetics – in order to actually ensure equal opportunities of blind and partially-sighted persons.

2.6.2 Package leaflets in formats appropriate for blind and partially-sighted patients

The requirement for making available the package leaflets in formats appropriate for the blind and partially-sighted patients will surely be very valuable to increase the options for a reasonable number of patients to get informed about the medicinal products they are taking or intend to take and to enhance the knowledge about these preparations. As outlined in section 2.5.1 *Potential approaches for implementation in the pharmaceutical industry*, this approach is feasible only in cooperation of the pharmaceutical associations with the pharmaceutical industry to make the best benefit, which will surely not be reduced to blind and partially-sighted patients only.

In a second step pharmaceutical companies could even improve their web sites according to the requirements of the German “Barrierefreie Informationstechnik-Verordnung (BITV)”, which is a supplement to the German “Behindertengleichstellungsgesetz (BGG)”, dated 27.04.2002 [43]. Although it is compulsive for web sites of the authorities of the German Federal administration only, some pharmaceutical companies, e.g. Pfizer Pharma GmbH, have already revised their web sites to comply with these particular German requirements and offer their services for a wider range of patients [44].

In addition, it has been proposed not only to present package leaflets in large print or in audio formats, but to offer them in sign language via the internet also. The pharmaceutical company Pfizer Pharma GmbH has placed a virtual package leaflet on its website detailing some general aspects for the various sections of a package leaflet in sign language [45].

Nevertheless, it seems worth discussing whether exceptions for the requirement of making package leaflets available in formats suitable for blind and partially-sighted patients should be implemented as it has been the case for Braille labelling (see section 2.5.1.1.3 *Potential shortcomings of the RLS-project*). As discussed in this section, this would surely be of help for a number of very small or medium-sized enterprises (SME), especially when they are concentrating on a small range of products that are produced in small quantities only. In addition, it seems appropriate to introduce exemptions for medicinal products used by healthcare professionals only, at least for those which are used at intensive care units only in contrast to e.g. vaccines or comparable preparations. However, any exceptions are of help for pharmaceutical companies only, if a common approach is reached and endorsed by all European member states.

In summary, the new initiatives as set out in the European Directive to provide equal opportunities for blind and partially-sighted patients are noteworthy means to improve

the situation especially for those patients. Nevertheless, as detailed above, the implementation of these requirements demands a meaningful sense of proportion between the needs and benefit of the patients and the supplemental burden for pharmaceutical companies. Moreover, it deserves a common European approach to weigh out the eligible interests of the patients versus those of the marketing authorisation holders; a number of potential points of interest to work on has been worked out as part of this thesis.

3 READABILITY OF PACKAGE LEAFLETS OF MEDICINAL PRODUCTS FOR HUMAN USE

3.1 Regulatory and historical background

3.1.1 Situation in Germany

With the first German Drug Law, dated 1976, coming into force in 1978 [46], marketing authorisation holders have been obliged to provide a package leaflet for each medicinal product in Germany. However, responsible marketing authorisation holders equipped their products with package leaflets already prior to the implementation of the AMG. With the second amendment of the German Drug Law in 1986 [47] the German “Fachinformation” (summary of product characteristics) had been introduced as source of information for the healthcare professionals, whereas the package leaflet should turn more patient-oriented.

The fourth amendment of the German Drug Law in 1990 required the complete declaration of all ingredients of a medicinal product [48].

An important change concerning the contents of package leaflets was introduced with the fifth amendment of the German Drug Law in 1994 [49], explicitly detailing the sequence of the particulars in the package leaflet as well as adding various data, such as information for special patient groups, e.g. children, use during pregnancy and lactation, potential effects on ability to drive and using machines etc. In fact, expanding the contents of the package leaflets was not necessarily assessed to be of mere benefit for the patient as at the same time it was intended to keep the information for patients rather tight to improve the comprehensibility.

The tenth amendment of the German Drug Law was especially meant to address the criticism of the European Commission on the German re-registration procedure [50]. In order to improve transparency, for all medicinal products not finally assessed by the competent Higher Federal Authority the following had to be included in the package leaflet: “This medicinal product has been placed on the market under the statutory transitional regulations. Official testing to determine pharmaceutical quality, efficacy and safety has not yet been concluded.” (§ 109 (1), 2, AMG).

Finally, with the fourteenth amendment of the German Drug Law [7] further changes were introduced in terms of labelling of medicinal products and the package leaflet and summary of product characteristics to comply with the requirements of the European Directive 2001/83/EC, as amended, which includes the adaptation of the German provisions according to the QRD-templates in addition [51].

The requirements for information on medicinal products in the German Drug Law are laid down in sections 10, 11 and 11a of the AMG: § 10 details the labelling of finished medicinal products (information to be presented on the container and outer wrapping,

where used), § 11 depicts the requirements of package leaflets and § 11a finally details the expert information, which corresponds to the summary of product characteristics.

3.1.1.1 Purpose of package leaflets and liability aspects

The purpose of the package leaflet is not defined in the German Drug Law. According to the accompanying commentary by Kloesel / Cyran the aim of the package leaflet is to provide the patient any information that is relevant for the proper use of the medicinal product (posology, dosing regimen etc.) and to inform about any risks related to its application (contraindications, special warnings, undesirable effects etc.) [52].

In addition, it is the responsibility of the information officer (see § 74a AMG) to ensure that the package leaflet corresponds with the content of the marketing authorisation and that no misleading statements form part. This is of particular importance since an incorrect or even missing package leaflet presents a severe matter of liability. The liability aspects as detailed in § 84 AMG apply also if a person is killed or the body or the health of a person is substantially damaged due to information provided in the package leaflet (or labelling or summary of product characteristics), which does not comply with the current medical expertise and knowledge. Consequently, the marketing authorisation holder has to decide for any new potential risk for a medicinal product whether this has to be labelled and addressed in the information texts. As a matter of fact, the length of package leaflets has increased enormously especially with regard to the sections undesirable effects, contraindications and special warnings and precautions for use [53, 54]. A further intensification resulted from the “Zweites Schadensersatz-Änderungsgesetz” (amending act for damages), dated 19.07.2002. This amendment comprises revised rules for burden of proof as well as considerable further rights to be informed for the patient in case of any damage due to a medicinal product [55].

3.1.2 Situation in Europe

The second main pharmaceutical Directive 75/319/EEC did not require the package leaflet as mandatory for the European member states [56]. However, any package leaflet used at that time had to comply with the requirements of this Directive. Obligatory use of the patient information leaflet had primarily been defined on European level with the European Directive 89/341/EEC, which had to be transformed into national law till 01.01.1992 [57]. Since Germany had already introduced this obligation as part of the second amendment of the AMG, only slight changes as regards contents were necessary [53].

Further information on the details required for the immediate and outer packaging as well as the package leaflet was provided with the Council Directive 92/27/EEC, dated

31.03.1992 [58, 59]. Article 6 of the said Directive demands a package leaflet for all medicinal products intended for the information of the users unless all the information required is directly conveyed on the outer or immediate packaging. In addition, it was already pointed out that the package leaflet shall be drawn up in accordance with the summary of product characteristics but using the specific order as described in article 7. The Directive emphasised also that “... *the package leaflet must be written in clear and understandable terms for the patient and be clearly legible in the official language or languages of the Member State where the medicinal product is placed on the market. This provision does not prevent the package leaflet being printed in several languages, provided that the same information is given in all the languages used ...*” (article 8).

In the subsequent years, the development of contents and presentation of the package leaflets was mainly based on European requirements and legal standards and was subject to continuous adaptations in order to create uniform claims for all European member states. Especially the Quality Review of Documents Group (QRD-group), a working group of the European Medicines Agency (EMA), publishes new standards for the creation of package leaflets on a routine basis (including adaptations for labelling and summary of product characteristics) [51]. Although adherence to these QRD-templates (current version 7.2, dated October 2006 for centralised procedure; current version 1.2, dated October 2006 for mutual recognition procedures (MRP), decentralised procedures (DCP) and referral procedures) is not mandatory, marketing authorisation holders are obliged to adhere to these [59, 60].

3.1.3 Requirements for package leaflets and main objections

In fact, the package leaflet constitutes one of the main sources of information for the patient when using a medicinal product in addition to the education by the attending physician. The major advantage of the package leaflet is that of permanent information which is constantly available for the patient. However, sovereignty of the consumer and in particular of the patient is not only dependent on correct and extensive information presented in the package leaflet, but its content has to be readable, understandable and valuable for the user, i.e. the patient. The challenge is to impart useful, understandable information on labels and leaflets and thus facilitate patient and prescriber education toward safe and effective drug therapy. This is of particular importance as medicinal products are not only dispensed from professional outlets and by pharmacies but in many countries they are also sold in non-professional outlets including grocery shops, supermarkets, gasoline stations and other retail outlets. Consequently, these products are sold without the benefit of professional advice to the patient who must rely solely on information as part of the label and the package leaflet only [61].

However, package leaflets have always given reason for discomfort and therefore provide room for improvement. Some sections of the package leaflet are often difficult to understand for the patient. Information is frequently given in scientific language in order to fulfil regulatory requirements. Package leaflets have also been judged to be more appropriate for medical staff and the authorities rather than the patient. However, it is the patient who needs to know and understand the benefits as well as the risks of its medical treatment [62]. In the following, only a small number of surveys is summarised, nevertheless giving an impression of the major weak points of package leaflets and the patient's conception of them.

It has been complained that leaflets are prepared with particular attention to technical aspects such as quality of printing, photographs and illustrations only. Such considerations are admirable but must come second to the clear presentation of information to actually reflect the particular needs of their target population [63].

In addition, a survey of representative customers in pharmacies in Germany in 2002 by Bayer Vital and the "Zentrum für Arzneimittelinformation und Pharmazeutische Praxis" (ZAPP) revealed that the patients long for having additional information and explanation that is not adequately and sufficiently addressed in the package leaflets at the time of the survey. The majority of patients (67 – 75%) wish to receive further details on dosage and method of administration, compatibility with other medicinal products and food ingested concurrently as well as side-effect profile. In addition, the interviewees criticised the use of technical medical terms even though these were followed by an explanation in plain German. It was felt to be preferable for the German expression to precede the Latin term, where such technical terms had to be used at all. The list of active ingredients and other ingredients also caused comprehension problems for many of the interviewees, even prompting requests for these to be omitted completely. Common criticism of the deficiencies of many old-styled package leaflets were the use of technical terms, the information overload, the small print size and the overall unclear arrangement of some package leaflets [64, 65].

A different survey in Germany in 2000 by Fuchs et al. discovered a number of further shortcomings, e.g. some package leaflets missed information concerning experiences and data for use in children and elder patients. It was often complained that the posology was not described clearly and precisely enough, e.g. package leaflets stated the amount of active ingredient to be taken in milligram but did not specify the respective number of dosage units or the volume to be applied. Lacking information which kind of liquid should be used for administering the medicinal product and whether intake in combination with a meal exerts any influence was criticised. Most of the package leaflets checked contained non quantifiable phrases such as "high doses" or "application for

longer time”, leading to the conclusion that they are of limited value only and might even be misleading for the patient and / or his caregivers. Six out of the 68 package leaflets examined even quoted controversial information.

Deficiencies that are often expressed are related to the general presentation of the package leaflets, e.g. the print size is judged insufficient while the package leaflet as such is too lengthy [66]. This has been confirmed by the results of an investigation of the “Wissenschaftliches Institut der AOK”, WidO, in 2005 where the patients interviewed stated that package leaflets are an important information tool, however, they are judged as being too long, incomprehensible, and even leading to uncertainty [67].

3.1.4 Readability guidelines on European level and in Germany

Being aware of various shortcomings of the presentation and constitution of package leaflets with regard to their acceptance and comprehensibility, improvements and general guidance have been published on European and German level in the past.

In 1998 the Pharmaceutical Committee of the European Commission published “A guideline on the readability of the label and package leaflet of medicinal products for human use” coming into operation in January 1999, after having started the discussion in the working group in May 1996 [68]. The purpose of the guideline is to provide guidance on factors which influence readability. Primary objective of this guideline is to ensure that the label and package leaflet are readable. For that purpose the guideline details general items for safeguarding readability such as print size (e.g. characters of at least 7 point Didot for the label and of at least 8 point Didot for package leaflets) and type, print colour, syntax and the properties of the paper used. In general, overlong sentences (i.e. more than 20 words) should be avoided; enumerations should be presented by use of bullet points with each bullet point including a minimum number of words only.

In principle, an active and direct style for the package leaflet should be used, by placing the verb at the beginning of the sentence. Where explanations are given for the instructions, the instruction should come first. Annex 1a of the above mentioned guideline includes a model leaflet according to the recommendations of the said guideline with additional background information to be found in Annex 1b.

The guideline already depicted that for a product administered by a health professional, information from the SmPC for the health professional only (instructions for use, special precautions for disposal) could be included at the end of the patient leaflet in form of a tear-off portion, to be removed prior to giving the leaflet to the patient.

The MHRA issued an additional “Best practice guidance on labelling and packaging of medicines” in June 2003 [69] to expand a set of principles that had been agreed by the Committee on Safety of Medicines. The aim of the guidance is to help to ensure that the critical information necessary for the safe use of the medicine is legible, easily accessible and that users of medicines are assisted in assimilating this information so that potential confusion and errors are minimised. This guidance also details additional national requirements to be followed such as that the full name of the medicine should appear on at least three non-opposing faces of the pack to aid accurate identification and that the posology of the product has to be stated on the pack when it is intended for self-medication. In addition, packs should include sufficient space for applying the dispensing label and, in general, a user test was deemed desirable to ensure the maximum clarity of the critical information. It is interesting to note that a number of the considerations as detailed in this British guidance have been incorporated as part of the European Directive 2004/27/EC.

The readability guideline, dated 1998, however, does not only detail general recommendations of how to present labels and package leaflets but describes in Annex 2 a method as an example for actually testing the readability of the leaflet. Whereas the primary objective of the guideline is to ensure that the label and the package leaflet are readable, it is acceptable for a package leaflet, which achieves an acceptable level of performance in a readability test to deviate from the rest of the guideline.

Being indicative for readability testing the test method based on the approach taken in Australia’s requirements for consumer medicine information is described [70]. This Australian approach is a diagnostic procedure with people tested being preferably from the population at risk for the specific medicinal product to be evaluated (for details see section 3.2 *Consultation with target patient groups by interview technique based on the “Australian method”*).

In December 1999, the QRD-group of the EMEA recommended that a readability test should be performed on the version of the package leaflet submitted as part of the centralised procedure applications [71]. The test should also be conducted after a significant amendment to the text of a centrally authorised package leaflet. However, marketing authorisation holders were not obliged to carry out a readability test and present the results of the respective test as part of the marketing authorisation application. Nevertheless, the readability tests and their outcome were assessed positively as some European countries such as the Netherlands even requested a readability test as part of the mutual recognition procedures [64].

With Directive 2004/27/EC [1], amending Directive 2001/83/EC [72], however, the significance and the new insights gained when performing readability testing have been

newly implemented and addressed in article 59 (3): “... *The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use...*”. In addition, article 61 (1) requires that the marketing authorisation holder submits results of such user tests with target patient groups to the competent authority for consideration as part of the approval of the package leaflet.

For Germany, these requirements have been implemented in § 22 (7) AMG with the 14th amendment of the German Drug Law (“... *In the case of medicinal products intended for administration to human beings, the results of evaluations of the package leaflet conducted in collaboration with patient target groups shall also be submitted to the competent Higher Federal Authority ...*”) [7].

As additional changes have been introduced by the amended Directive with regard to labelling and package leaflets, a revision of the so-called “readability guideline” was required. A draft “Guideline on the readability of the label and package leaflet of medicinal products for human use” has been published in September 2006 [3] detailing general aspects of how to ensure and improve the readability of the label and the package leaflet by giving general style suggestions, detailing specific recommendations for blind and partially-sighted patients and providing guidance concerning consultations with target patient groups for the package leaflet (i.e. the former separate guidances on these two topics have now been incorporated in the capacious “readability guideline”). It can be determined that the draft guideline followed the report of the British Committee on Safety of Medicines Working Group on Patient Information “Always read the leaflet” [73], first published in 2005, in numerous sections and recommendations.

Main objective of the draft “readability guideline” is to give advice in improving the quality of leaflets and packaging. Nevertheless, there are a number of recommendations which are difficult to be implemented by pharmaceutical manufacturers and will lead to major implications for the layout of packaging components and package leaflets, especially considering multi-lingual packages or small pack sizes. Therefore, further revision by the European Commission is an important factor to make the guideline both beneficial and realisable.

Additional guidance has been published by the German BfArM in its notification “Bekanntmachung von Empfehlungen zur Gestaltung von Packungsbeilagen nach § 11 des Arzneimittelgesetzes (AMG) für Humanarzneimittel (gemäß § 77 Abs. 1 AMG) und zu den Anforderungen von § 22 Abs. 7 Satz 2 AMG (Überprüfung der Verständlichkeit von Packungsbeilagen)”, dated 30. November 2006 [74]. Main items of this national German guidance are to provide recommendations for the design and presentation of patient-oriented package leaflets as well as the examination of their readability. The notification itself follows the details and explanations as given per the European draft “readability guideline” and even refers to it.

Selected important aspects of the European draft guideline and the German notification will be presented and discussed in the following sections.

3.2 Consultation with target patient groups by interview technique based on the “Australian method”

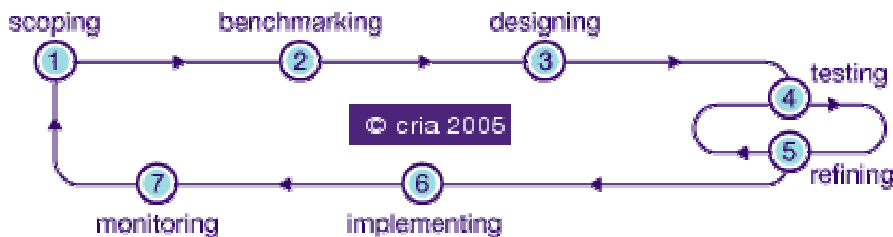
Package leaflets are an integral part of the marketing authorisation of a medicinal product. They are important for the safe use of a medicinal product and are the “public face” of the SmPC and of the marketing authorisation holder.

Apart from the information provided by the health care professionals, i.e. medical practitioners and pharmacists, the package leaflet serves to ensure that medicines are used both safely and appropriately. This is of particular importance as the extent of information provided in a PL is inevitably much more widespread than the information provided to the patient as part of the consultation with the health care professionals. Besides from being a legal obligation to marketing authorisation holders, the user testing of package leaflets can be a crucial process to guarantee that the message contained in the PL is clear and understandable to the patient. Therefore, the provision of good quality patient information is intended to supplement and not to replace the advice given to patients by health professionals.

Diagnostic user testing was first pioneered in the early 1990s in Australia. It is a performance based, flexible development tool which identifies barriers to people’s ability to understand and use the information presented and indicates problem areas which should be rectified. It is particularly useful as part of a leaflet development process and aims to identify whether or not the information, as presented, conveys the correct message to those who read and should understand it. The user testing according to Professor David Sless from the Communications Research Institute of Australia [75] is a “performance based” testing and therefore differs from the “content based” approach used in the past, where a checklist is applied to ensure that the correct information is present [76]. If testing reveals barriers to understanding, carefully considered changes to the leaflet will be needed to improve it [77].

According to the understanding of David Sless, the text of a medicine information has three main functions – headings for navigation, instructions on what to do and explanations to help understand why to do it. When issuing a label or package leaflet, the designer must approach the writing and the presentation of each of these functional elements as one integrated task because readers do not separate content and form [75]. The information design process behind this approach can be illustrated in different stages (see *Figure 3-1*), which will be detailed in section 3.2.1 *Description and evaluation of procedure and major steps*.

Figure 3-1: Stages of information design



According to Sless and Shrensky usability and usability testing is too easy to see the “scientific” nature of this activity as a validating principle in itself. However, when looking at the outcome rather than the means, usability testing is an expression of respect for others and a social desire to be friendly and helpful to others, which explains the often used phrase “user friendly”. Taking the latter into consideration, usability testing can be much more clearly seen as an act of courtesy, involving people who will have to use the material in the process of developing and refining that respective material, i.e. the package leaflet in this regard. Therefore, user testing is legitimated by its social purpose rather than the methods it uses.

3.2.1 Description and evaluation of procedure and major steps

At first glance, user testing sounds rather simple – to check whether people can find and understand key messages in a leaflet. In fact, there is much more to it than that. It covers one-to-one, face-to-face, structured sets of interviews, involving at least 20 participants reflecting the population for whom the medicine is intended [3, 77].

The term “user testing” will preferably be used throughout this thesis although the term “readability user testing” would be more appropriate as the test procedure is meant to examine the legibility as well as the comprehensibility of a package leaflet [78]. Legibility is a result of text size, line length, layout and structuring. The good usage of icons and pictograms has a noticeable effect on the ease of finding – and to some extent on the understanding. In contrast, comprehensibility ensures that a package leaflet is understandable so that it qualifies as a good information source for the patient. Short sentences, the use of lay-terms and a personal addressing enhance this comprehensibility. For the discussion of the outcome of a user test, the presentation of both legibility and comprehensibility is therefore important.

3.2.1.1 Performing of and preparation for the test

User testing of package leaflets may be done by the marketing authorisation holder or applicant directly, however, in most cases a suitably qualified company or service provider will perform it on behalf of the applicant. In fact, a number of contract research organisations (CRO) have emerged specialising on user testing or have added this tool to their scope of services since user testing has become mandatory as part of the European Directive. In most cases it is not meaningful for pharmaceutical companies to conduct these tests with their own personnel and have them trained accordingly but it is more feasible to rely on the services of a specialised CRO [79].

Selection of contract research organisations (CRO)

Selecting the CRO should be done carefully with respect to the expertise and the scope of services provided. Due to the importance and the impact of the outcome of user testing, it is recommended to choose CROs, which have been certified according to ISO 9001 Quality Assurance System to ensure a standardisation of processes, increase in product and service quality and to meet the needs of the clients, i.e. the pharmaceutical industry.

A detailed and binding project schedule including clear definition of the patients being suitable for the respective medicinal product should be set up with the CRO to depict the different steps of the project, the responsibilities and the respective timelines and to ensure product confidentiality. As a general rule, the duration for a user testing of one medicinal product is approximately 7 -10 weeks including costs of 10,000 – 15,000 € up to 30,000 €.

Selection of the country for performing the test

It is normally sufficient to undertake patient consultation in one European language, which can be any of the official European languages, according to the draft “readability guideline”. The results of the user testing, however, have to be presented in English language for the centralised, decentralised and mutual recognition procedure, or in the national language in case of a national procedure to be accepted as part of the marketing authorisation application.

The statement in the current draft “readability guideline” that testing in one language will normally be sufficient is quite vague and therefore a more specific definition would be appreciated detailing in which cases testing in one language will not be considered adequate and sufficient.

Although patient consultation in any official European language is allowed and sufficient, most applicants decide to perform their user tests in the United Kingdom for the following reasons:

-
- United Kingdom has been kind of a pioneer in developing additional guidelines and publishing details on the performance of user tests and has been rather strict and demanding concerning the necessity of (additional) local user testing and the basic need for user testing.
 - In the centralised, decentralised and mutual recognition procedure, only the English language version of the package leaflet is agreed during the scientific assessment of the EMEA and the competent authorities involved in the procedure, respectively. The quality of translations into the various languages, however, should be the focus of a thorough review by the applicant or marketing authorisation holder once the package leaflet has been properly tested. Consequently, it lends itself to use the English version of the package leaflet for performing the user testing.
 - The MHRA requires all marketing authorisations submitted before 01.07.2005 to comply with the necessity of user testing by 01.07.2008 [80].

Hence, not surprisingly a large number of CROs offering services for user testing are located in the United Kingdom.

Selection of interviewers

Selection of the interviewers conducting the face-to-face interviews for the user consultation is a very sensitive item and has to be exercised with caution. As the test will mainly depend on the interviewer, a standardisation of the interview technique and the surrounding is highly recommended. This kind of user testing is clearly dependent on these parameters and has to be judged as a definite weakness of this type of testing. Although the marketing authorisation holder does not have direct influence on selection of interviewers by the CRO, it is worth to analyse the selection criteria for interviewers applied by the CRO.

The interviewers have to be chosen carefully for that they are able to respond to the different interviewees. As the interview is a situation where empathy, spontaneity and sovereignty are essential, the interviewer must be patient, possess a good knowledge of the human nature and should have excellent observational and listening skills. This is of particular importance as the interview situation incites nervousness, potentially leading to an excited participant who is prone to errors. Interviews should therefore take place in a calming surrounding to reduce this nervousness, which is essential especially for older and reserved patients.

Ideally the writer of the package leaflet will carry out the interviews, or occasionally accompany the interviewer during testing, in order to enable direct transfer of learning during the interviews. As this will not be feasible for most interviews carried out, an

optimal exchange of information between the interviewer at the CRO and the marketing authorisation holder has to be ensured.

Preparation of the package leaflet

Prior to performing the user testing, the package leaflet has to conform with the current requirements as detailed in the European Directive 2001/83/EC, as amended (e.g. Article 63 (2) “*The package leaflet must be written and designed to be clear and understandable, enabling the user to act appropriately.*”), and the respective QRD-templates. Depending on the scope of services provided by the CRO, the current package leaflet including the mock-up or specimen⁸ may be checked by the CRO by help of medical writers, communication scientists and linguists. Based on this first evaluation and advice, further improvements may be implemented in the package leaflet prior to initiating the actual user testing. However, the marketing authorisation holder and the CRO have to be careful that changes in compliance with current EU requirements and QRD-templates are implemented only. This is of particular importance in case the CRO selected mainly focuses on linguistic review and advice for revision of the package leaflet prior to the actual user testing.

Unfortunately, the draft “readability guideline” requires “... *to test the readability of a specimen with a group of selected test subjects.*” In fact, it would be highly appreciated from a practical point of view that testing may be performed on mock-ups also as testing on specimens is technically quite difficult and cost-intensive, especially when the user testing has not been successful and needs further repetition with revised package leaflets. Although the handling of a specimen for user testing by the patient better mimics the actual use of a package leaflet, the additional benefit by testing on specimens is deemed not too comprehensive to justify the use of specimen only.

3.2.1.2 Selecting participants and recruitment

Selection of participants

The draft “readability guideline” requires that a range of different types of people who are able to imagine needing to use the medicine are included in the test procedure. In case of testing medicines for rare diseases, the people included should preferably have or have had the respective illness.

⁸ A mock-up is a copy of the flat artwork design in full colour presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three dimensional presentation of the label text is clear. The mock-up is generally referred to as a paper copy and not necessarily in the material of the sales presentation.

A specimen, however, is a sample of the actual printed outer and immediate packaging materials and package leaflet (i.e. the sales presentation).

In addition, further demands on subjects to be interviewed are detailed as follows with regard to the fact that the information which can be used by the least able will be beneficial for all users:

- Particular age groups such as young people and elderly people (especially if the medicine is particularly relevant to their age group, i.e. the target age groups are preferred)
- New users or people who do not normally use medicines
- People who do not use written documents in their working life
- People who find written information difficult.

In fact, selection of adequate test persons for the user testing is rather challenging especially with regard to the target group for the respective indication and, even more difficult, in case the medicinal product has multiple indications [80]. To find a reasonable balance, it might be helpful to select participants according to the patient populations chosen for the clinical trials as part of the marketing authorisation application.

In a number of cases, it will be helpful that the target group of test persons is discussed with the competent authority, i.e. the EMEA or the reference member state (RMS). This is of particular value and necessity in case of medicinal products which can be applied by health care professionals only as the choice of the population consulted has to be defined and explained in the final test report submitted to health authorities. The draft “readability guideline” details in chapter 3, section 7: “... *The people who are likely to rely on the package leaflet for a particular medicine will depend upon a number of factors and may include carers (e.g. parents, partners, friends, as well as nursing assistants) rather than patients if the medicine is generally intended for administration by someone other than the patient...*” [3]. It is worth noting that the MHRA gives somewhat inconsistent advice on this particular item in its “Questions and Answers” papers. The paper in June 2005 details that there may be special indications e.g. Alzheimer’s disease where the care-givers may be the appropriate target group for user testing [80], whereas the additional publication dated June 2006 records that “...*health care professionals and other staff / people who routinely work with medicines information must be excluded to avoid bias...*” [78], which means that care-givers would not represent adequate test persons.

The German BfArM, however, accepts a reasonable number of health care professionals as part of the test group in these cases. A more consistent approach of the different European member states, especially with regard to the definitions of the target patient group as set in the European draft “readability guideline” would therefore be highly appreciated to ensure the acceptability of the results of user tests regardless of the member state where they have been performed.

In addition, further obstacles have to be faced in case of medicines intended for treatment of young children or patient groups being impaired and therefore depending on medical care by care-givers such as patients with Parkinson's disease. Furthermore, difficulties are present in case the patients to be included for user testing already suffer from visual impairment due to their underlying disease and have difficulties in concentrating on reading anyway.

Recruitment of participants and data security

In fact, patient recruitment is one of the main factors contributing to the informative value and success of the user testing and is therefore very time-consuming. Patient selection for participating in the user testing has to be well balanced with regard to age, gender and educational level. This is particularly challenging when testing has to be carried out for medicinal products addressing rather specific indications or rare diseases.

CROs for user testing have implemented adequate networks for medical recruiters such as physicians, pharmacists, self-regulating communities and nursing staff. They may enter personal data of their patients and customers in a database, such as Mediclarity [81], provided that the respective patients have filled in a personal data sheet beforehand and have consented by signature that they may be contacted for user testing purposes. In addition, interested persons may directly enter their data in the data base when being interested in voluntarily participating in a user test.

These potential participants are informed via mailings etc. about upcoming user tests, whereas this kind of advertisement does not require any official approval by authorities. Using such data bases for patient recruitment offers the advantage that assignment of patients and volunteers for the different tests can be recorded and therefore prevents from including the same persons repeatedly. In order not to bias the results by training effects of the patients participating in user tests, an appropriate time period should be ensured between the attendance of different user tests. The MHRA suggests that participants should not be used more frequently than once every six months [78]. In addition, a fully operational database helps to effectively manage interview dates and to keep the usually tight project timelines for user testing.

Once having fulfilled the inclusion criteria outlined above and being selected as a participant for a user testing, the patient and the recruiting person (physician, pharmacist etc.) will normally receive appr. 20-50 € for compensation purposes.

Since data security must be warranted, every participant has to sign a declaration of confidentiality. On the other hand the participant's personal data are made anonymous as it is done for clinical trials. Some CROs conducting user testing offer video recording of the test sessions, which is especially helpful for the sponsor who will in most cases

not be able to join the testing (although attending the interview is of benefit for the applicant, see section 3.2.1.1 *Performing of and preparation for the test*), provided, of course, the written consent of the participants is available.

3.2.1.3 Sample size and use

Only small numbers of participants are needed. At its best, a total of 20 participants will be required to meet the success criteria (see section 3.2.1.4 *Success criteria*). The following approach is proposed by the draft “readability guideline”, Annex 1, section 3 [3]:

- A pilot of around 3-6 participants to test that the questions will work in practice. Having gained experience with user testing and the class of product tested, a number of 2-3 participants may even be sufficient for the pilot test.
- The pilot test is followed by at least two rounds of 10 people each, reviewing the results after the first round and making any necessary amendments to the package leaflet.
- Tests have to be repeated until satisfactory data from a group of 10 participants are available.
- A final test of a further 10 participants is required to check whether the success criteria are also met in this further group of 10, resulting in an overall number of 20 participants.

A pilot test with a small group is highly recommended especially in case of complex indications and package leaflets which have not already been tested to assist risk minimisation of failing the user test criteria. A pilot test should also be carried out in case the package leaflet is very long or contains complicated but indispensable terminology due to the indication. It has also been proven meaningful to conduct a pilot phase in case a new layout has been introduced for the leaflet. Based on the outcome of the pilot test, which should be summarised in a report, further adaptation of the package leaflet will most likely be required and will usually be proposed by the CRO and discussed with the sponsor (the marketing authorisation holder) resulting in a revised package leaflet.

In contrast, there are some situations where a pilot phase might not be absolutely necessary, e.g. when a previously tested layout is used that already achieved very good finding results for the information in former user tests or when the package leaflet has previously been tested and needs retesting due to a variation.

Consequently, when planning a user testing, it is very valuable to spend sufficient time on the strategy of the conduct and set-up of the user testing to avoid unnecessary test rounds (including time and expenditures).

For the subsequent main study, a group of 10 participants will be involved assessing the revised package leaflet. In case of a successful outcome of this first round (for requirements see section 3.2.1.4 Success criteria), a second round including further 10 participants will follow. Being successful with the second round also, the user testing can be considered finalised provided a suitable final report has been issued (see section 3.2.2 *Structure of testing report for marketing authorisation application*). Having failed however in the first cycle, which results in further revision of the package leaflet, involves repeating the complete test procedure with 10 patients twice in order to have an overall number of 20 participants that met the success criteria.

Bearing in mind the complexity of setting up and conducting an interview-based user testing compared to the fact that diagnostic testing does not result in statistically significant data [80], it would be highly appreciated that in case the first round with 10 responders passes the benchmark outlined in the guideline, but revisions to the package leaflet are nevertheless recommended, this should be possible without the need to run two further test rounds to finally ensure that 20 respondents have reviewed exactly the same package leaflet. In such a situation, the improvement between the first and the second round would be an extra improvement only, which is actually not particularly required. Otherwise it may easily lead to a huge number of testing rounds which are not deemed helpful for gaining any additional information.

3.2.1.4 Success criteria

The statistical evaluation of a user testing carried out by the interview-method as described is specified in the current draft “readability guideline”: “... *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 ...*” [3]. Using different methods of testing apart from the interview-method may require different success criteria, which will be considered by the competent authorities on a case-by-case basis.

It is essential to note that the success criteria have been tightened compared to the ones applied by Sless and Wiseman according to the Australian requirements: 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 [68]. These Australian success criteria have also been detailed in a “frequently asked questions” paper of the German BfArM, dated 30.11.2006 [82], which has been published after the European draft “readability guideline” – and is therefore less stringent than the official European standards.

Tightening of the success criteria has also been defined as part of the additional notifications of the MHRA [78], requesting that each question must perform satisfactorily which is a different approach as the one demanded in the current draft “readability guideline”. The MHRA considers it inappropriate for data to be accumulated and for one or more key messages not to be found and understood by participants.

As a consequence, each single question of the test protocol has to be listed separately for each patient concerning legibility, i.e. finding of information, and comprehensibility, i.e. understanding of the content. Thus, in case one single question is not adequately found by 2 out of 20 patients tested, the user test would have already failed. This approach seems not to be helpful or adequate as a general binding rule, especially when considering the enormous differences in terms of the length and levels of difficulty of different package leaflets depending on their indication and mode of application (e.g. when comparing a package leaflet for an analgesic like aspirin with an anticoagulant like phenprocoumon or a powder inhaler to medicate patients suffering from asthma). For the example stated above, i.e. one question has not been found by 2 out of 20 interviewees, it should be applicable and sufficient if comprehensibility is evaluated for the remaining $n=18$, provided that no major general concerns exist with the package leaflet in question.

In addition, those 2 patients not having located the information in the package leaflet could be advised where to find the respective statement(s) and comprehensibility for this question could be tested accordingly. Final evaluation would then be performed for all participants included.

According to the experiences gained by now with user testing by help of the interview technique, it is not unusual that different subjects have difficulties with different questions. For that reason, the overall assessment of the quality of a package leaflet should be more important including justification and explanation for deviations on particular questions than mere achievement of certain scores. Failure to individual questions should not be considered as a failure of the overall test as a basic principle.

Generally, it would be highly appreciated if competent authorities would handle the success criteria somewhat flexible by taking into consideration the requirements of the patient group in question – and, in addition, if a common understanding could be reached on such an approach for all European member states to avoid any supplementary national requirements unnecessarily complicating the process.

3.2.1.5 Test protocol

The test protocol required for user testing is to some extent comparable to the study protocol for a clinical trial during the development of medicinal products. Each medicine tested requires a separate test protocol for user consultation. The whole test shall be designed to last for about 45 minutes up to 60 minutes at most to avoid tiring of the participants. All important and difficult issues of the package leaflet shall be addressed by adequate questions including a set of expected correct answers. It has been proven helpful to address appr. 12-15 questions as part of the questionnaire directly related to contents of the package leaflet and to add further 3-5 questions on the subjective impression of the participants related to the appearance and overall design of the leaflet.

The performance of the interviewer is a crucial factor for the outcome and usability of the interview (see section 3.2.1.1 *Performing of and preparation for the test*). It is his responsibility to make the patient feel comfortable during the interview and to observe the behaviour of the patient, e.g. how the patient handles the package leaflet, if he gets lost or confused during the interview and especially at which step or question etc. The interviewer will ask the questions verbally and will encourage the participant to answer in his own words without simply reading off the information from the package leaflet, i.e. the test should be performed in a conversational manner. On the other hand, the interviewer should invite the interviewee to look up the requested information in the PL rather than to answer from memory only.

It appears quite controversial that the interviewer shall record the answers given to the questions by the participants but at the same time shall adopt a conversational manner as requested per the draft “readability guideline” [3]. In fact this procedure will more or less interrupt the flow of the interview and is judged to have a negative influence on the atmosphere, especially as the whole interview may go along with nervousness from the patient’s side. It would be appreciated if this requirement would be softened so that only important answers have to be written down including in particular those where the patient has difficulties with the package leaflet.

In addition, provided that the participant has given his consent beforehand, a video could be recorded for archiving purposes.

Question requirements

It has to be ensured that the content related questions reflect specific issues and key messages for the safe and effective use, especially critical safety issues with the medicine, as well as compliance issues to ensure the validity of the user test. Consequently, as a first step, the key safety messages have to be identified. Creation of the questionnaire requires particular attention and sufficient time as not all information of the package leaflet, especially for lengthy ones, can equally be represented in the

questionnaire due to the time constraints of 45 to at most 60 minutes per interview. When having developed all possible and reasonable questions for the particular product, they should be ranked first whether they address important or less important items. In a second step, the most appropriate questions will be selected from this assortment of potential questions whereas it has to be ensured that all matters dealing with important messages of the package leaflet are actually included in the final questionnaire. Development of the questionnaire and the decision on the final version should be done in mutual agreement between both, CRO and applicant.

The questions should preferably present a balance of general and specific issues. A general issue would be what to do in case a dose is missed, whereas a specific one could relate to a side effect which is specific for that medicine. The questions should appear in a random order, i.e. different to the sequence of information presented in the package leaflet. In addition, the wording should be different to the one used in the leaflet. This is to test whether the patient actually finds the requested information and understands it.

In order to make the patient feel comfortable during the interview, it has been shown advisable to implement questions reassuring the participant at the beginning, such as “On a scale of 1 to 10 (1 = very incomprehensible, 10 = very comprehensible), how comprehensible do you find the patient information leaflet?” or “Are there any negative aspects concerning the patient information leaflet? How could we improve them?”.

It has to be stressed that defining the correct questions is of huge importance for the outcome of the user testing. Experience has shown that the participants often quote the name of the drug substance although the question was to indicate the name of the medicinal product. For preparations requiring particular storage conditions (e.g. “Do not store above 30°C.”) it has been shown inadequate to ask how the medicine should be retained as participants may misunderstood the question and may answer that the medicine has to be kept out of the reach of children – which in fact is not wrong but does not reflect the necessities of the particular preparation.

Again, these examinations underline the need of an adequate assessment of the results obtained via the user testing by the respective authorities as the robustness and absolute significance of the statistical evaluation as a single success criterion remains questionable (see section 3.2.1.4 *Success criteria*).

Considering package leaflets of medicinal products which are applied by health care professionals only, e.g. infusion solutions, it is proposed to reflect whether user testing could be improved by questions that differ with respect to the interviewee and his educational background. As discussed in section 3.2.1.2 *Selecting participants and recruitment*, inclusion of caregivers, nurses etc. may be acceptable for those

preparations. This should enable the applicant to incorporate a separate subset of more difficult questions in the questionnaire which are especially addressed to those participants having additional background information in order to receive a meaningful conclusion for this sub-group of interviewees.

3.2.2 Structure of testing report for marketing authorisation application

According to the Notice to Applicants, Volume 2B, the “... *information from the applicant regarding the “user consultation” performed together with the presentation of results, or a justification not performing such consultation, is to be included in this section for all new applications and for relevant post-authorisation applications introducing significant changes to the package leaflet...*” has to be included in section 1.3.4 *Consultation with Target Patient Groups* [83] of the Common Technical Document (CTD).

The information to be included in such a testing report should be structured as follows [3]:

1. Product description
2. Consultation or test details, such as
 - Method used
 - Explanation on the choice of the population consulted
 - Language(s) tested
3. Questionnaire (including instructions and observation forms)
4. Original and revised package leaflets
5. Summary and discussion of results (subjects’ answers, problems identified and revisions made to relevant package leaflet section)
6. Conclusion

In addition, it may be helpful for the assessor to start the report with a concise overall summary of 2-3 pages of the test strategy, the target patient group definition, the questionnaire development, information on the pilot test (if applicable) and the main test and finally the overall conclusion prior to depicting the sections above in detail.

Detailed information on the choice of target patient group as well as inclusion and exclusion criteria (especially when changes are implemented for the main test cycles) and the recruitment of the patients should form part of the report. This should preferably include a tabulated listing of demographic data of the patients included, e.g. gender distribution, age groups distribution, information on education levels (e.g. secondary school, A-level, degree or higher degree, other qualifications etc.).

Demonstration of the results obtained has to be performed in accordance with the requirements of the draft “readability guideline”, especially focussing on the statistical evaluation (see section 3.2.1.4 *Success criteria*). This should include the mapping of the success of finding and the success of understanding the respective information per single participant in form of a histogram. Comparing these displays with a mapping of information found and comprehended for each question related to the overall number of participants (in %) seems reasonable to get a more comprehensive insight of the outcome of the interviews and the user test in general.

Secondly, the ease of finding the information should be rated by the participants as “very easy”, “easy”, “difficult”, “very difficult” or “not found” for each of the various cycles of user testing. Having gained experience with user testing and the respective distribution for the quality of finding information in package leaflets in general, any deviation from the usual distribution gives additional input for potential drawbacks of the package leaflet.

Apart from mere evaluation of the actual answers of the participants to the questions asked, it is of significant importance to consider any additional comments made by the participants, regardless whether positive or negative aspects, e.g. “The structure is great but subheadings could also be highlighted.” or “All important messages should be posted at the beginning of a section.”.

In any case, it is important to manage any identified weaknesses and to clearly demonstrate the improvements that have been implemented during the different user test rounds.

Assessment by competent authorities

The assessment of the test reports by the competent authorities and the EMEA, respectively, will consider the items listed above and will comprise e.g.

- Technical assessment, i.e. assessment of the recruitment and the questionnaire used regarding number of questions and contents enquired, assessment of interview aspects and conduct
- Evaluation of responses, i.e. acceptability of qualitative evaluation of responses and evaluation methodology
- Data processing, i.e. recording and documenting of data
- Quality aspects, i.e. evaluation of diagnostic questions in accordance with the draft “readability guideline”, evaluation of layout and design regarding design principles
- Diagnostic quality / evaluation, i.e. have weaknesses been identified and if yes, have they been adequately addressed
- Final overall conclusions [84].

The outcome of this assessment will be reflected as part of the assessment report (AR) for the final decision whether the marketing authorisation may be granted or not.

In addition, the Dutch Health Authority, CBG – MEB, has published two checklists on its web site, one of them dealing with the contents of a user testing report [85] and one detailing the criteria for the assessment of a package leaflet readability test after 1 November 2005 [86]. The latter comprises a detailed checklist of the requirements as laid down in the “readability guideline”, which are verified whenever an applicant provides a test report. Although the checklist does not reflect the most recent changes implemented in the current draft “readability guideline”, it nevertheless represents a very helpful tool for setting up, conducting and evaluating a user test for a package leaflet from an applicant’s point of view. It can be assumed that other European competent authorities may have implemented a similar checklist or catalogue of requirements for internal use following this Dutch example.

3.3 Description of further methods for testing

3.3.1 Standardised interview in writing according to Fuchs

In contrast to the interviews specifically concentrating on the particular package leaflet as it is done for the Australian method, standardised interviews in writing may be used according to Fuchs as an alternative approach. This model is based on the fact that meaningful questions can be issued which are applicable to all medicinal preparations. In contrast to the conventional face-to-face interviews this model shows the advantage of not being influenced by any interviewer [82].

The performance of the test is similar to the Australian method despite of the face-to-face interview which is replaced by a questionnaire to be filled in writing by the participants. The test persons also have to state demographic data such as age and gender and shall describe their general impression of the respective package leaflet. The questions have to address all three types of information, i.e. very important information (e.g. contraindications, posology, therapeutic indication), important information and less important information.

The test group should include at least 15 participants and at least 80% of the answers given have to be correct, which is in accordance with the Australian model.

This standardised interview according to Fuchs has already been successfully validated by addressing items such as choice of questions, legibility and comprehensibility of information, selection of participants and consistency of the data obtained [87]. The validation has been performed by cross-over testing original package leaflets as used by the pharmaceutical companies versus model package leaflets of the same preparations but rephrased by the group of Fuchs. Testing of both was performed with a four weeks time interval. Rephrasing of the original package leaflets was done according to pre-

defined quality criteria (total number of 104) which had to be met entirely. The quality criteria encompass e.g. “dosage instructions are available”, “all dosage instructions are given as number of tablets or capsules or as volume, drops or amount of the drug”, “maximum daily dose is included” etc. [88]. The size of the leaflets nevertheless did not exceed two pages of DIN-A4, especially by avoiding repetition of information and making use of bullets for presenting data.

The advantage of this test approach is to have a validated system in place with a high degree of standardisation which does not require an interviewer and consequently is less accident-sensitive. Due to the standardised questions and standardised performance of the interview which results in a simplified evaluation procedure, the reliability of the test system is huge. Common acceptance of this test method by the European authorities would surely be of great benefit for the pharmaceutical companies especially with regard to the increasing number of user tests required due to variations or line extensions of existing marketing authorisations. By now, a small number of successful user tests according to the standardised procedure of Fuchs have been reported. As opposed to the original aim of the proceeding of Fuchs the standardised interview questionnaire was not filled in by the patient himself but was used as part of a face-to-face interview of the patient.

Nevertheless, it remains questionable whether a description of the contents of a package leaflet will actually be possible by using two DIN-A4 pages only for each medicine without shortening and / or distorting the information. In addition, a careful check is recommended whether any particular issues form part of the package leaflet which require particular attention apart from the standardised questions, especially with regard to key safety messages.

3.3.2 Communication science based approach

User testing may also be performed based on communication science based cognitions analysing a package leaflet by help of a software programme. These programmes check a number of criteria which correlate with a good comprehensibility of the package leaflet. The big advantage of these systems is that they are independent of any influences by test persons [82].

An important prerequisite for successfully using these methods is that a qualification / validation report is available detailing that the communication science based approach equally leads to good results as compared to the interview technique according to the Australian method (see section 3.2 *Consultation with target patient groups by interview technique based on the “Australian method”*). This report has to form part of the submission to competent authorities as well as a detailed justification why this approach

is assessed suitable for the respective package leaflet. Nevertheless, there may also be cases where an additional user testing by help of interviewing patients will be required and where competent authorities will decide on a case-by-case basis whether a communication science based approach is solely sufficient.

Usually, these test methods do not only evaluate and analyse existing package leaflets but may especially be used for improving them. Test parameters that are checked include two different items, i.e.

1. formal, typographic and visual parameters such as paper quality and weight, folding, colours and fonts used
2. linguistic and structural parameters such as syntax, diction, grammar, record length, number of subordinate clauses etc.

Typically, Times New Roman as a serife-font is proposed, but Arial is also widely used and recommended to enhance the readability especially of longer texts. Regarding syntax it is suggested to follow a record length of not more than 20 words and to include two subordinate clauses at most. Active voice and the avoidance of negations also help to improve readability of texts. Where medical terms need to be used, they should follow a lay term only which is widely understood by the patients. Further items dealing with the readability of a text are checked by help of these software programmes. In general, quite a huge amount of these items to be tested has also been addressed as part of the currently available draft “readability guideline”.

Once having checked a package leaflet with these programmes, further optimisation of the wording and layout can be done by using these systems, provided that set-points for the different parameters to be tested have been pre-defined [89].

The considerable advantage of this communication science based approach is the multitude of parameters that can be checked in parallel. The objectiveness of the test outcome has to be emphasised as it may not be influenced by interviewers or patients and therefore ensures a high reliability. However, the test system lacks any conclusions related to subjective impressions conveyed by patient interviews. Using this procedure for improving the package leaflet prior to an interview with patients according to the Australian method, seems reasonable especially with regard to quite comprehensive package leaflets. Despite of the objectiveness of the test method, user testing of package leaflets by help of the communication science based approach only may arouse difficulties in acceptance by the authorities as the individual feedback of patients is missing. Though, this system should be acceptable for user testing of rather short package leaflets of medicinal products with a manageable safety profile or instead of a bridging report when testing the leaflet for a medicine where package leaflets of the same drug class have already been successfully user tested.

For the sake of completeness it should be mentioned that first steps concerning readability of package leaflets have already been addressed in the past by using so-called indirect methods, i.e. reading scores or readability formulae. Historically, readability formulae have been used to match the reading difficulty of health information with the reading skills of users. Most formulae combine several parameters such as the length of sentences and word frequency and rarity. Examples include the Flesch Reading Ease Index⁹ [90, 91] and the Simplified Measure of Gobbledygook (SMOG)¹⁰ Test [92].

Such tests are based solely on content and focus on words, rather than the patients who need to understand the contents. No account is taken of the complexity of meaning within a piece of text, the layout of the leaflet, size of text or other factors which could affect the users' ability to assimilate the information.

Readability testing alone by help of readability scores only can therefore not be considered as appropriate as sole evidence in meeting the legal obligation of the marketing authorisation holder to undertake user testing of their package leaflets. It is noteworthy that a leaflet written backwards will have the same readability "score" as when written forwards (same words and same sentence length) [76] underlining the restricted significance of such tests.

3.3.3 Communication and discussion with specific patient groups

A further approach for conducting user testing of package leaflets is the discussion with specific patient groups such as patient groups dealing with diabetes, HIV-infections, hemophilia and also patient groups dealing with rare diseases, e.g. mucoviscidosis and sarcoidosis [84, 93]. Reading the package leaflet, however, is only one item for these patients concerned for being informed about their disease. Apart from reading package leaflets, they are usually well-informed about their disease, its consequences for plans for life and additional medical aids that are available. In addition, they gather information by their physicians, pharmacists, via the internet and, of course, via specific patient groups as their main task is to provide appropriate information.

⁹ The output of the Flesch Reading Ease formula is a number from 0 to 100, with a higher score indicating easier reading. The average document has a Flesch Reading Ease score between 6-70. The formula reads as follows: $206.835 - (1.015 \times ASL) - (84.6 \times ASW)$, where:

ASL = average sentence length (the number of words divided by the number of sentences)

ASW = average number of syllables per word (the number of syllables divided by the number of words).

A score of 0 would be practically unreadable and a score of 100 would be easy to read for any literate person.

¹⁰ The SMOG grade (Simplified Measure of Gobbledygook) is: $3 + \text{square root of the polysyllable count}$ (words of three or more syllables per 30 sentences). SMOG grades 13-16 indicate the need for college education, 17-18 the need for graduate training, and 19 and above the need for a higher professional qualification.

These specific patient groups are of help for user testing as they may impart appropriate patients for the user consultation and may give additional advice on particular requirements of the respective patient group and their caregivers, where necessary. The benefit of working together with specific patient groups for user consultation is that the typical environment of the patients concerned can be taken into account and that their particular needs may be identified easier as opposed to the selection of a randomised patient group only (see section 3.2.1.2 *Selecting participants and recruitment*). A particular advantage provided by using patients of these patient groups is that the actual patient population is envisaged reflecting also common concomitant diseases these patients may suffer from.

It has to be kept in mind that these potential advantages imply a number of disadvantages at the same time jeopardising a reliable outcome of such kind of user testing. These patients are well informed about their disease and available medicinal information via the internet and other sources of information so that the results of user consultation with these patients will most likely not reflect a more general situation. The latter makes the assessment for both, the pharmaceutical company and the assessors at the authorities, difficult or even impossible.

Nevertheless, conducting user consultation with specific patient groups should be an alternative applicable for particular situations, which require adequate explanation by the marketing authorisation holder. In addition, a combined approach by using specific patient groups and volunteers also as one test group or as a staged testing system might be of help to avoid bias as outlined above.

3.4 Timing of submission to the competent authorities

The member states and the EMEA, respectively, have agreed to accept text proposals for the SmPC, package leaflet and labelling in English as part of the marketing authorisation application [94]. In any case it is sufficient to undertake user testing on leaflets drawn up in one language and the testing may be done on leaflets prepared in any official language of the EU, which must not necessarily be the language of the RMS in case of mutual recognition or decentralised procedures. Results of these tests have to be presented in English to permit the assessment of the test by RMS and CMSs as necessary (see section 3.2.1.1 *Performing of and preparation for the test*). The same applies for type II variations and renewal applications (for further details see section 3.5 *Justification for waivers and for bridging studies*).

For all application procedures (except the mere national ones) it is the English language version of the SmPC, package leaflet and labelling that will be agreed during the

scientific assessment by the competent authorities involved. According to article 28 (2) and (3) of Directive 2001/83/EC, as amended, [72] products authorised through the MRP and DCP will result in a harmonised package leaflet between member states, so that there will be no national package leaflets in Europe for products authorised via MRP or DCP in future. Consequently, the situation has become similar to the one for the centralised procedure.

Finally, high quality translations of the agreed SmPC, package leaflet and labelling should be submitted at the latest five days after the end of the procedure of assessing the application for a marketing authorisation or variation. The responsibility for the production of faithful translations, however, rests with the marketing authorisation holder in consultation with the national competent authorities and the EMEA, respectively. It is helpful that already during the drafting of the original package leaflet efforts are made to ensure that it can be translated from the original to the various national languages in a clear and understandable way. It is important that the outcome of the user consultation is correctly translated into the other languages, whereas a strict literal translation is not prescribed to avoid any unnatural phrases which are not understandable for the patient in the different countries. Regional translation flexibility is therefore allowed, whilst maintaining the same core meaning [3].

Whereas for the centralised procedure¹¹ [95, 96] and the mutual recognition procedure the results of consultation with target patient groups have to be submitted as part of the marketing authorisation application or as part of a variation or renewal application (except for waivers in distinct cases) for marketing authorisations granted prior to 30.10.2005 respectively¹², the situation is different for applications as part of a decentralised procedure, which has been newly implemented with the Directive 2004/27/EC.

For the decentralised procedure there is an additional possibility that applicants may use the “clock stop” period to undertake consultation with target patients groups and therefore it may be possible to address this matter within the procedural timeframe of the authorities’ assessment [97]. Already prior to the submission the applicant is encouraged to discuss with the RMS whether user consultation is required for the respective application or whether an expert justification for its absence is likely to be

¹¹ It should be noted that, if not included in the initial submission, the results of user consultation or any further clarification, as requested, will have to be submitted as part of the answers to the list of questions at Day 121.

¹² Detailed guidance on practical considerations concerning the phasing in of Directive 2004/27/EC and timing of submission of user test reports for medicinal products authorised before the date of entry into force of the new legislation are presented in the „Questions and Answers“ Papers of the Heads of Medicines Agencies and the EMEA, respectively. Details on the time schedules shall not be presented as part of this thesis.

acceptable. At day 105 of the assessment phase I, the applicant will receive the comments from the RMS and all CMSs involved in the procedure. Regardless whether at this stage a consensus has already been reached that the medicinal product is approvable and only minor issues have to be addressed or whether no consensus had been reached at this point, the applicant has to reply to the open issues during the clock-off time. He will respond to the questions, provide updated SmPC, package leaflet and labelling proposals and will also undertake initial or further user consultation of the package leaflet considering all comments received from the different European member states.

The assessment of the results of user consultation or the justification for its absence will then form part of the Draft Assessment Report prepared by the RMS between day 106 and 120.

This approach clearly bears advantages for the applicant as it helps to avoid unnecessary user testing and to save time and expenditures for draft package leaflets which are almost routinely subject to more or less comprehensive changes during the assessment period by the authorities. Once having revised the package leaflet according to the initial comments from the member states during the assessment phase I, it is still questionable and unclear whether the results of the user testing of the original leaflet version are yet applicable. Depending on the nature of the comments received, the applicant will most likely decide to repeat a complete user consultation for the revised draft package leaflet in order not to endanger the chances of success for granting the marketing authorisation.

Of course, it is meaningful for both, applicant and assessors that the user testing is already conducted with the initial proposal of the package leaflet submitted as part of the marketing authorisation application. The input of the test results at this point of time, however, remains equivocal at least for those cases where the member states will require substantial revisions, such as listing of additional possible side effects, changes in special warnings or even addition of contraindications and restrictions to or rephrasing of the therapeutic indications. Due to the fact that the user consultation shall especially address the key safety messages, any outcome of the first testing would become useless for such an example.

Nevertheless, it has to be doubted whether all member states will actually validate a submission for a decentralised procedure in case the results of consultations with target patient groups are missing. If a submission is judged invalid by a single member state and requires the results of user testing beforehand, the applicant will lose time as he has to withdraw the submission and file it again when having the user testing results available.

As long as the definitions and expectations for waivers and bridging studies on the one hand and definition of significant changes that require (repeated) user testing in case of a variation on the other hand (see section 3.5 *Justification for waivers and for bridging studies*) are not yet clarified and agreed by the European member states, the approach for the decentralised procedure remains a critical one from the applicant's point of view.

In general, it would be highly appreciated if clear input from the competent authorities and / or the European Commission would be provided under which circumstances the results of the user testing are still applicable even when changes in the leaflet are introduced during the assessment of a marketing authorisation application. In addition, facilitations should be defined in case an additional user testing is required due to the authorities' assessment. The items could be comparable to a compilation for cases where only single sections of a package leaflet are changed which is also recommended as part of this thesis (see section 3.5.2 *Bridging studies*). In any case, the problem of additional and repetitive user testing should be addressed and resolved on a preferably European level.

A similar situation applies for the required harmonisation process of package leaflets between member states for products authorised through the mutual recognition and / or decentralised procedures according to articles 28 (2) and 28 (3) of Directive 2001/83/EC, as amended. Again, there is considerable uncertainty about the optimal timing of the user test during the harmonisation process. After a user test potential significant changes to the leaflet resulting from the harmonisation process may again have to be tested. However, user tests are an integral part of the marketing authorisation application dossier. This restricts the user testing to a timeframe before all harmonisation changes are made to the package leaflet.

It has to be kept in mind that the package leaflets will in fact be harmonised after such a process but not necessarily be identical as the contents of the package leaflets may differ with regard to the name of the medicinal product, the marketing authorisation holder, the legal status (OTC or prescription only), the package sizes etc., so that as a consequence the layout will necessarily be different. The same applies to the newly introduced "blue box concept", presenting specific national requirements for the package leaflet and labelling as part of a mutual recognition or decentralised procedure [98, 99], which adds to a different appearance and layout as a matter of fact.

3.5 Justification for waivers and for bridging studies

In general, performing the user testing or another justified consultation method will be essential prior to granting or varying any marketing authorisation, regardless whether centralised, mutual recognition, decentralised or national procedures are applied. For all marketing authorisations granted after 30.10.2005, all requirements set out in Directive 2001/83/EC, as amended, i.e. especially articles 59 (3) and article 61 (1), apply. For changes to an existing package leaflet, the necessity for conducting user consultation depends on the extent and scope of the changes (see section 3.5.1 *Waivers*). For medicinal products for which the marketing authorisation has to be renewed according to the new legislation, the package leaflet should be in line with the requirements of article 59 of Directive 2001/83/EC, as amended. However, consultation with target patient groups is not considered as a condition of renewal, and the applicant may ask for submission of the respective results afterwards in accordance with an agreed timeframe with the respective authorities [94].

According to chapter 3 of the draft “Guideline on the readability of the label and package leaflet of medicinal products for human use”, dated September 2006 [3], a new user consultation for a medicinal product will always be necessary in the following situations:

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

In contrast, the evidence of user consultations on similar package leaflets according to article 59 (3) and article 61 (1) of Directive 2001/83/EC, as amended (see section 3.1.4 *Readability guidelines on European level and in Germany*) may be used where appropriate. This will be considered acceptable only based on a sound justification by the marketing authorisation holder, e.g. in the following cases:

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

However, for referencing to a representative sample of package leaflets which comply with the revised legislative requirements, the types of package leaflets have to be chosen carefully to be representative of one or more of the following considerations:

- Recently approved package leaflets for a corresponding medicinal product
- Reflect complex issues of risk communication which may need careful handling
- Medical terminology which requires detailed explanation.

Despite of these enumerations in the draft “readability guideline” by the European Commission, a number of questions still remains unsolved, especially when taking into consideration the additional national guidance by the European member states, which are explicitly mentioned in the draft “readability guideline”, i.e. “... *The Member States or the European Medicines Agency will have considered other aspects in relation to consultation or user testing and usability of packaging leaflets and additional guidance is available or under development concerning...*” [3].

The draft “readability guideline” details that if user consultation has been performed on a package leaflet in the old QRD-template, there is no need for retesting when the leaflet is updated to be in line with the new QRD-template. The British Health Authorities, MHRA, however, go further and require that submission of data demonstrating compliance with article 59 (3) of Directive 2001/83/EC, as amended, is necessary in case the order of the information in a package leaflet is changed to comply with the new requirements of the said Directive, i.e. to comply with the new QRD-templates [80, 100]. Although the MHRA does not demand complete user testing but allows for bridging studies [101], this example alone already demonstrates that despite of having a European guideline detailing the requirements of the European Directive, additional national guidance may be in contrast to the demands of other member states, aggravating the demands posed on marketing authorisation holders to comply with the current rules of the European Directive. The MHRA also reserves the right to request a user test where there is any doubt regarding the usability of the information presented with an application [77], which hinders planning of submissions of marketing authorisation applications and variations involving the United Kingdom as reference or concerned member state.

3.5.1 Waivers

Although the draft “readability guideline” gives some advice under which circumstances a separate user test is not required but reference to already approved and recently tested package leaflets is possible, it seems doubtful whether the definitions as detailed will be sufficient to clearly define situations where waivers will be accepted, especially with regard to potential different national interpretations and notifications. In any case a detailed and thorough justification has to be submitted to the competent authorities.

The same applies for the necessity to provide further results for user testing in case of variations to existing package leaflets. According to the draft “readability guideline” the need for user consultation covers in principle situations where significant changes are made to the package leaflet. In fact, the term “significant changes” is rather undefined and needs further specification to support applicants with traceable and unambiguous provisions, especially in order to avoid national solo attempts. Nevertheless, in case of

uncertainties the pharmaceutical companies are asked to decide in favour of patients' interests and conduct patient consultations.

In its Questions and Answers document on the implementation of the new legislation [94] the CMD(h) details in question 19 that the absence of test results from consultation with target patient groups can be justified by referring to another tested package leaflet (the so-called reference package leaflet) provided that the key messages for safe use have been adequately addressed. It is required that the package leaflet and the reference PL are similar in content, and the design and layout should also be considered as part of the justification. An adequate justification which critically appraises the similarities / differences between the submitted and the reference PL and which addresses the relevance of test results for the reference PL is demanded. Furthermore, the applicant has to provide a critical comparison of the design and layout of both package leaflets.

The justification for absence of consultation with target patient groups including reference to other tested package leaflets is not restricted to new applications, but may also be applied in case of renewals and variations which necessitate user testing.

In any case, adherence to the harmonised Quality Review of Documents (QRD) templates only will not exempt from the obligations to undertake user testing or a different suitable form of user consultation.

In its "frequently asked questions" paper [82], the German BfArM detailed the following situations where a sound justification for a waiver could be considered adequate: (a) reference to an identical or almost identical package leaflet of the originator, which has already been tested, (b) slight changes with respect to an already tested package leaflet. Indicating that the respective preparation has already been marketed for a long time period without any negative experiences is per se not sufficient as basis for a waiver. Nevertheless, it would be worth granting a waiver in cases where a medicinal product has been marketed for a long time in nameable amounts, having only a few, but slight side-effects, being easy to administer and not having shown reasonable signals or hints in the safety assessments of the periodic safety update reports (PSUR).

Making reference to a package leaflet of the originator that has already been tested requires, however, that package leaflets which have undergone user testing are appropriately marked and are made available as part of a transparency initiative. For the moment, it remains unclear how this approach can be reached in an acceptable way for both, originator and generic companies. In order to avoid unnecessary duplication of user testing, a passable solution for both parties would be highly appreciated.

A similar situation applies to the more than 600 modeltexts (“Mustertexte”) in Germany, which are published on the web site of the German BfArM [102], based on § 28 (2) 3 of the German Drug Act, and are widely used especially with regard to national German marketing authorisations. For the time being, the modeltexts have not been user tested. In the meantime, a number of them have been adjusted to comply with the requirements of the current 14th amendment of the German Drug Law and the QRD-templates also. There has been no common approach published of how the user testing of the currently available modeltexts could be handled in an efficient and transparent mode. It is deemed to be a feasible way if user testing of all modeltexts would be conducted as part of a common project headed by the German pharmaceutical associations. The relevant fees could be distributed among the pharmaceutical companies being members so that all marketing authorisation holders could benefit from the tested modeltexts. Modeltexts already successfully user tested could be marked accordingly in the respective BfArM database. This would prevent multiple user testing of identical texts conducted by different companies at the same time –most likely with different outcome. For the latter approach it would have to be scrutinised from a legal point of view whether a revised modeltext based upon a company-driven user testing may be published on the respective BfArM web site so that other companies could use them.

In any case, each pharmaceutical company would have to perform an additional separate user testing addressing the company layout and general design of package leaflets once to supplement the above data as a bridging report (see section 3.5.2 *Bridging studies*).

A further item requiring legal assessment and input is the question whether a generic marketing authorisation application according to article 10 of Directive 2001/83/EC, as amended, [72] may refer to the successful user testing of the originator – without knowing its content – in order to request a waiver for his own application or to submit a bridging test for his company-specific package leaflet design only. Literally taken, the European Directive allows reference to the non-clinical and clinical data of the originator. It remains questionable, however, whether this implies reference to the respective user testing of the package leaflet, especially as the test results form part of module 1 of the common technical document (CTD).

3.5.2 Bridging studies

In contrast to the possibility of requesting a waiver for providing the results of consultation with target patient groups, the CMD(h) does not give any advice for situations where a bridging study might be adequate and sufficient.

In its guidance on the use of bridging studies the MHRA describes the term “bridging” as to apply to leaflets which are sufficiently similar in both content and layout [101]. This is due to the fact that minor changes to content or layout of a document can already impact adversely on the readability. In bridging, a successful user test on one package leaflet (the “parent” PL) can be used as a justification for not testing other similar leaflets (“daughter” PLs). However, since the design and layout of the information is crucial of how the information is used and understood, “daughter” PLs should be of the same design, layout and writing style as the “parent” PL as one prerequisite in order for bridging studies to be successful. According to the understanding of the MHRA, a common design and layout includes the following aspects:

- Font and font size
- Headings and sub-headings including consistency of placement
- Package leaflet dimensions including whether the document is laid out in portrait or landscape format
- Use of colour and choice of colour
- Style of writing and language used
- Layout of critical safety sections of the package leaflet
- Use of pictograms.

In contrast, in a bridging study the key messages for safe use for both the “parent” and “daughter” PL need not be identical, provided that high profile safety issues are included in the key points tested for each daughter PL.

Bridging studies can be used under the following circumstances in case the target patient populations are similar:

1. Line Extensions

Bridging is normally acceptable for package leaflets of the same drug substance for different strengths or routes of administration, provided that the “parent” PL is the one which contains the more / most complex information for the patient. Different criteria, however, have to be applied in case of significantly different methods of administration. In these cases a “double” bridging could be applied, i.e. bridging with a package leaflet with the same drug substance and bridging with a package leaflet with an identical administration method in addition.

2. Medicines in the same “drug class”

Bridging will normally be acceptable for package leaflets for medicines in the same therapeutic class where the clinical information set out in the package leaflet is similar, again, provided that the format and layout of the package leaflets are identical. As a matter of fact, this means that the “daughter” PL has to be revised and drawn up in the format and layout as the respective “parent” PL.

Medicines which are considered a “group of medicines” in terms of therapy area, but in fact contain many different medicines going along with different modes of action etc. have to be considered on a case by case basis.

In contrast, in therapy areas with many different medicines with differing modes of action but the key issues around safe use are much less critical, bridging may be acceptable, e.g. cough preparations, antacids, vitamins.

3. Same Key Messages for Safe Use

4. Same Patient Population

5. Combination medicines

Generally, the package leaflet for the combination medicine should be considered as the “parent” PL for the purpose of bridging to the individual component “daughter” PL. Vice versa, it may be possible to use the individual component package leaflets as the “parent” PLs and bridge to the combination PL as the “daughter” provided any differences in layout and length of the combination PL have been subject of successful user testing within the company portfolio.

6. Short package leaflets for medicines with minor therapeutic actions

Examples would be water for injection, aqueous cream, hypromellose eye drops.

7. OTC medicines with a variety of minor components

Remedies and OTC products with multiple ingredients can be bridged with package leaflets which have been successfully tested for the main active ingredient(s), e.g. compound analgesics based on paracetamol.

8. Pictograms

Pictograms used within a company house style will need to be tested as part of a user test. For bridging to encompass pictograms successfully the pictograms in “daughter” PLs should have the same design, dimensions and colours as those in the “parent” PL.

9. Bridging between companies

If a letter of access is provided, a second company may apply to use the same package leaflet as another marketing authorisation holder provided the content of the package leaflet (except for specific company information) is identical. However, in both cases the design and layout for the package leaflets concerned should be identical in all aspects as discussed above.

In general, the catalogue of requirements sounds both reasonable and challenging. In order to benefit from the bridging approach, pharmaceutical companies will have to check their entire product portfolio and should ask for support by skilled CROs to draw up an appropriate bridging plan, taking into account preferably the requirements as detailed by the MHRA. It is deemed wise to also list the European countries where marketing authorisations have been granted and check for any particular national requirements or experiences, especially with regard to sound justifications for bridging of user tests.

One main critical item will surely be assuring and demonstrating that the different package leaflets addressed by a bridging report are of the same design, layout and writing style. Although most companies have a corporate design for their package leaflets, there will be a number of reasons why the design is different throughout the company's portfolio. This might be due to very diverse therapeutic indications or diverse dosage forms, i.e. transdermal patches and powder inhalers often require additional illustrations and annotations to ensure a safe use of these products. Furthermore, companies dealing with OTC-preparations as well as prescription-only products will most probably use different designs for their package leaflets, especially in case additional information is included in the package leaflets of the OTC-preparations as it is assessed of help for the patient to give him some additional advice on his indisposition (e.g. sleeping pills, cough and cold medicines).

In addition, the writing style of package leaflets for OTC-preparations and prescription-only preparations will most certainly differ, not least due to the fact that alone the QRD-templates vary with regard to the opening remarks but also the sections dealing with side effects, precautions and warnings as well as contraindications will often differ in style since OTC-medicines normally do not entail so many and critical side effects and contraindications.

It would be highly appreciated if the acceptance criteria for waivers as well as bridging reports would be harmonised and detailed on a European level, giving binding advice to all European member states. Otherwise, it can be easily imagined that bridging studies may be acceptable and helpful for national authorisations within one country, however, without adequate influence and improvement for marketing authorisations covering more than one member state. A situation where any concerned member state (CMS) requires

a full or more comprehensive user testing instead of a bridging report as accepted by the respective reference member state (RMS) should be avoided for the benefit of both, competent authorities and pharmaceutical companies. The details concerning the requirements for same design, layout and writing style, however, should not be tightened extraordinarily to remove one further hurdle. In fact, the cultural differences within Europe with regard to layout and design have to be paid attention to and companies often face the problem that an identical layout will not be acceptable within all European member states (see section 3.4 *Timing of submission to the competent authorities*).

Furthermore, it is suggested that requirements should be detailed on a European level that revision of certain sections of a package leaflet only does not necessarily require a full user testing with at least 10 participants per test phase (see section 3.2.1.3 *Sample size and use*). In addition, a common approach for all European member states detailing which safety issues and changes for a package leaflet are assessed a critical safety issue and therefore require a full user testing is deemed of vital importance to avoid different understandings of the various competent authorities within a mutual recognition, decentralised or centralised procedure. This could be achieved following the “Guideline on the definition of a potential serious risk to public health in the context of Article 29 (1) and (2) of Directive 2001/83/EC” [103].

3.6 Fields of general improvement concerning package leaflets and critical items as per the draft “readability guideline”

According to an evaluation of the “Wissenschaftliches Institut der AOK” (WIdO) the central questions concerning the information content of package leaflets from the patients’ point of view are as follows [104]:

- Which medicinal product is concerned?
- What is the purpose of the medicinal product and which diseases can be treated?
- What has to be kept in mind prior to the treatment with the medicinal product?
- What has to be kept in mind during the treatment?
- How is the medicinal product applied?
- Which undesirable effects are possible, how can they be diagnosed and what has to be done in case of a side-effect?
- What else has to be considered?

In order to achieve an optimised package leaflet according to the needs of the patients, a number of points that could be addressed and / or should be critically assessed will be presented in the following sections.

3.6.1 Structure of QRD-templates

Although a lot of improvements have already been implemented concerning the structure and design of information texts and especially the package leaflet (e.g. readability guideline, QRD-templates), the headings in the QRD-templates and their order have still been shown to be difficult to understand for consumers according to results from user testing. In section 2. “Before you take / use the medicinal product X” of the package leaflet, the contraindications have to be listed as follows: “Do not take / use X, if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of X.” The other ingredients, however, are listed at the very end of the package leaflet in section 6. “Further information; What X contains” only. Already this example shows that the QRD-templates and the arrangement of the information is not yet of an optimum level.

It remains unclear how rearrangement or rephrasing of the headings or the standard statements as established by the QRD-templates due to the outcome of the user testing of a particular product will be assessed by the competent authorities. A suitable and comprehensible case by case evaluation would be considered helpful to provide appropriate certainty for the pharmaceutical companies.

In addition, it has to be kept in mind that a lot of patients usually do not read the complete package leaflet but refer to certain sections only, which they feel to be most important and relevant for their use of the medicinal product (e.g. dosage and method of administration, interaction with food). According to patients’ statements this applies e.g. in case of prescription-only medicines where they have been told to use the respective preparation by their physician. Although the draft “readability guideline” recommends avoiding repetition of information by cross-referring to information which is under another heading where this is appropriate, use of cross-references should be handled with care and a suitable balance should be introduced between unnecessary repetition of information and confusion on the other hand.

Taking these experiences into account, it is deemed helpful to also place the QRD-templates under user testing to achieve the best possible readability. In fact, as one result of user testing it has become apparent that patients often are not able to allocate the appropriate information to respond to questions dealing with contraindications as patients suspect the “worse” information as part of the section “undesirable effects”. According to the PAINT-study by Fuchs, the same problems apply for the section “posology” [59]. As one experience with user tests performed by now, it seems to be a rather common problem that the information presented in the leaflets is comprehensible as such, but is hard or even not at all traceable in the package leaflets tested, i.e. legibility is insufficient.

A similar attempt has only recently been proposed and published by the MHRA due to a survey of companies between 20.12.2006 and 11.01.2007 who undertake user testing on behalf of marketing authorisation holders [105]. Findings from this survey indicate that the wordings of many of the headings and subheadings in the QRD-templates are not well understood by patients.

3.6.2 Extent and preciseness of package leaflets

The extent of package leaflets has been continuously increasing within the last years, which is due to a variety of reasons, e.g. the dramatic growth of knowledge about medicinal products and the patients' right of comprehensive information including positive and negative findings as well as the liability issue with regard to the marketing authorisation holder (see section 3.1.1.1 *Purpose of package leaflets and liability aspects*).

Nevertheless, it remains doubtful whether the information to be included in the package leaflet as per the current requirements of Directive 2001/83/EC, as amended, is actually needed and, even more important, is of any additional help for the patient. According to the PAINT-study by Fuchs [59] patients judged the information on the manufacturer and the marketing authorisation holder as less important. While it is without question that these addresses have to be detailed due to legal aspects, it has to be analysed whether for centrally authorised medicines the listing of the addresses of the marketing authorisation holder or his representatives in all EU member states is actually of any added value for the patient. The same applies for the newly introduced requirement of stating the trade names of the medicinal product in all European member states where medicinal products authorised via the mutual recognition or decentralised procedure are marketed. It is to be questioned whether this additional information is of any additive value for the patient from a transparency point of view or whether it particularly contributes to the fact that the patient gets lost with the package leaflet.

Furthermore, it is of disadvantage that there is still no guidance available as to which and how much information the package leaflet shall contain. Due to this fact, the upcoming harmonisation procedures for package leaflets throughout the European member states concerned will become a rather thrilling experience, just as it is already the case in the European phase of mutual recognition and decentralised procedures. The expectations and requirements of the different European member states are still quite diverse concerning the extent of information, e.g. with regard to undesirable effects, which has triggered a number of referral procedures in the past.

Especially with regard to the presentation of undesirable effects in the package leaflet, there has been quite a lot of discussion to sort out the best approach for reporting.

Arrangement according to system organ classes (SOC) including differentiation according to frequencies has been shown to be misleading for patients. A common approach which has been proven successful during user testing, is the description of undesirable effects according to their frequencies, starting with the most frequent one. However, it has also been complained that the information about possible side effects and other warnings which EU law requires the package leaflet to include can be alarming to medicine users. For the presentation of the side effects, it has been suggested to state the most important information first. More importantly, a survey discovered that patients equate the verbal descriptors such as “very rare”, “common”, etc. to risk substantially higher than those defined in regulatory documents. Therefore, a number of different approaches have been published such as presentation of relative and absolute risk or use of diagrams etc. to give patients a clearer picture of the actual frequency [73].

The extent of package leaflets of products to be administered by health care professionals only, especially with regard to life-saving medicines, has always been a point of discussion. In fact, in case of emergency the attending physician will consult the package leaflet to rapidly look up or confirm the dosing regimen or interactions prior to administration as opposed to the respective SmPC – simply because of urgency. Although the QRD-templates allow including a separate section addressed to health care professionals only or even to attach a complete SmPC for these preparations, the flow of information is somewhat disturbed for the physician. Based on this fact, it would be worth discussing on European level whether the inclusion of health care professionals, at least to a certain extent, for user testing of these package leaflets could be accepted by all European member states. The health care professionals in fact are the ones who are the actual “users” of these preparations and this should be reflected as part of the user testing (see section 3.2.1.2 *Selecting participants and recruitment*).

3.6.3 Print size and design

The draft “readability guideline” recommends to use a font size of 12 point for the main body of the text and where practical a larger font size for headings, e.g. 14 points. For visually impaired patients the preferred font size should even be between 16 and 20. Italic fonts and underlining should be avoided as well as widespread use of capitals.

In fact, a font size of 12 point is desirable, however, it is not practical with regard to the amount of information that has to be included in a package leaflet. Readability is also dependent on the amount and size of paper the patient has to handle and especially to unfold and refold again for placing back the package leaflet in the respective folding carton. This is particularly important in case of multi-lingual package leaflets;

consequently, a moderate and meaningful balance should be established between the paper size and quality and font size on the other hand. Actually, package leaflets have usually been written in at least 8 point font size according to the readability guideline, dated September 1998 [68]; using a font size of 12 point type size would result in a 30 to 50 per cent increase in the length of the leaflet. These increased package leaflets will most probably lead to technical problems during manufacturing and to elevated, however, rather unnecessary extra costs. In most cases, the mechanical process of the package leaflet folding and introduction into the box during the production process will be compromised. In addition, it cannot be avoided that increase of the size of the package leaflets requires expanding of the secondary packaging also, which is allowed to a certain extent only due to the European requirements for bluff packages.

Reuptake of a minimum font size as required per the previous guideline is deemed important to avoid the above detailed problems and, in fact, user testing of the package leaflets using smaller fonts than 12 point will actually reveal any particular problems of the patients with regard to readability. As for those patients being visually impaired separate offers will have to be introduced by the pharmaceutical companies (see section 2.5 *Package information leaflets in formats appropriate for the blind and partially-sighted*), the needs of this patient group are already appropriately attended.

Since the widespread use of capitals should be avoided as per the current draft “readability guideline”, it is recommended to recheck the QRD-templates for the information texts preferably via user testing as the headings are printed in capital letters only (see section 3.6.1 *Structure of QRD-templates*).

Furthermore, the draft “readability guideline” details that line spaces should be kept clear and recommends that the space between one line and the next should be at least 1.5 times the space between words on a line. Again, this requirement will not only lead to space problems with regard to the package leaflets, but it has to be doubted that this will actually improve the readability. It is deemed more appropriate to clearly separate individual sections and paragraphs as opposed to printing the whole main body text with large line spaces.

A column format for the text is the preferred layout as it can help the reader navigate the information. In fact, first results of user testing have shown that patients feel more comfortable with landscape layout as opposed to portrait format, especially when printing the heading over the entire breadth as this resembles the typical appearance of newspapers, regardless of its standard.

Particular attention has to be paid concerning the use of booklets, i.e. additional information brochures that deal with supplementary information on the therapeutic indication, further recommendations of what else can be done except for medicinal treatment etc. These booklets – although not presenting the contents of a package leaflet – have to undergo user testing also. It is deemed important that mock-ups rather than specimen are applied for user testing of booklets. A clear separation of the sections, preferably by implementing page-breaks for each section, as well as a very clear arrangement and formation of the content seems to be necessary to make up a useful tool for patients. Whereas package leaflets themselves are often printed in two to three different colours only, the use of different colours and eye catchers as part of a booklet is assessed to be of value for the readability and legibility of these booklets.

3.6.4 Style

The draft “readability guideline” encourages to use an active style, to avoid repetition of information by cross-referring to other sections of the package leaflet, where applicable, and to translate any technical term into a language which patients can understand. The latter is highly recommended and could be approached by help of an equivalent to the existing Medical Dictionary for Regulatory Activities (MedDRA), an international medical terminology. Based on a common dictionary on European level, medicinal and technical terms could be allocated a particular lay term – to be translated in each European language - which should be used by all pharmaceutical companies to promote consistency and to aid production of clear and understandable package leaflets. Such a glossary of medical terms in lay language has already been suggested and a draft version has been published as part of the publication “Always read the leaflet” of the MHRA [73].

Such a common terminology would be of additional value especially for multimorbid patients requiring a number of different medicinal preparations and therefore having to face the same number of different package leaflets.

An advanced harmonisation of statements and wording proposals for the different sections of the package leaflets is deemed of help especially with regard to multimorbid patients but also with regard to pharmaceutical manufacturers. As it has been implemented for a number of sections in the SmPC (e.g. “Pregnancy and lactation”, “Effects on ability to drive and use machines” or “Preclinical safety data”), it would be appreciated if a similar approach with adequate wording suggestions for the package leaflets would be promoted on a European level. This could be of advantage especially with regard to the section “How to take / use the medicinal product”, pre-defined explanations for the administration of different dosage forms could be one example (i.e. administration of capsules in upright position, divisibility of tablets – where possible

[106], preparation of antibiotics as dry powders to be dissolved in water [107] etc.). This would also serve to avoid administration instructions such as “Take two tablets twice a day.” which has been proven to be misleading as most patients were of the opinion that two tablets should be taken per day [108].

At the very end, such a “harmonisation” could also be of added value for the PIM project (see section 2.5.1.1.1 *Technical aspects of the RLS-project*). In any case, such an approach would have to be handled with some margins and space left to adapt the wording where necessary.

3.6.5 Syntax

Apart from other items, the draft “readability guideline” recommends using simple words with few syllables in order to make the package leaflet understandable for persons with poor reading skills and / or poor health literacy also. In addition, the sentences should not contain more than 20 words and numerous subordinate clauses should be avoided.

Detailing the contents of a package leaflet in short sentences and addressing an adequate literacy level is undoubtedly very important to ensure comprehensibility of a package leaflet. However, a sentence length of not more than 20 words will not be applicable for all European languages. The German translation of an English sentence will in almost all cases be longer than the English original sentence. Especially when taking into consideration that faithful translations are required based on the English version as agreed during marketing authorisation procedures (see section 3.4 *Timing of submission to the competent authorities*), this requirement can not be strictly followed in all cases. Consequently, appropriate flexibility would be appreciated.

In the light of straightforwardness and convenience of the style the draft “readability guideline” recommends creating package leaflets based on the fact that information which can be used by the least able will be beneficial for all users. However, it remains doubtful whether the contents of a package leaflet will in all cases be demonstrable without being inaccurate by using a style that addresses the least able also. This request is also reflected in the inclusion criteria for the selection of patients for the user testing. In fact, it is questionable whether inclusion of patients not using written documents in their working life (which is nowadays rather improbable anyway) and patients who find written information difficult apart others adequately mirrors the mean powers of comprehension of the patients.

It may be assumed that these recommendations go back to the British publication “Always read the leaflet” [73], which details an evaluation for England and Wales stating that nearly half of all adults aged 16-65 were classified to have a skill level expected of

11 year olds. A separate British survey came to the conclusion that highly educated patients do not mind if instructional materials are oversimplified for them [91].

Actually, it is hard to believe that such a simple style and wording will be of benefit for the average of the potential patients and, even more important, will be accepted at all as patients might miss an adequate seriousness of the wording. Interestingly enough, Kenny et al., United Kingdom, found out that "... a style which is too simple could sound patronizing and may lack interest and 'authority'..." [109].

These divergent surveys underline the necessity to reconsider the requirements and in particular the inclusion criteria for patients in order not to impede the positive attempts of the consultation with target patient groups.

3.6.6 Print colour and symbols / pictograms

The draft "readability guideline" recommends dark text to be contrasted against a light background as a general rule, in rare occasions the opposite may be adequate to highlight particular warnings. Different colours may be used for displaying headings or important information clearly and easily recognisable, whereas red colour print should be reserved for very important warnings only.

Although red colour print will not be detectable for colour-blind people, it nevertheless seems to be worth considering a survey on European level concerning the use of colour and the potential increase of readability of the package leaflet. This is due to the fact that colour is both a way of emphasising a message and of communicating in an emotional manner in a presumably universally way. Since it has been criticised that the information in package leaflets is often understandable but hard to find, associating certain sections of a package leaflet with corresponding colours might be of benefit to improve their readability (see section 3.6.1 *Structure of QRD-templates*).

A first investigation has been conducted in Italy [110] to evaluate the attitude of patients towards modifications in terms of colour apart from other typographical variations. Most of the participants, i.e. 65.7%, did not like the coloured package leaflets, however, patients with a higher educational level were more favourable towards a coloured leaflet. As this study was focused on Italy only, it would be worth examining whether the outcome reflects the overall picture for Europe as well. It should not be the aim to construct painted package leaflets reminding of advertisements rather than serious information, but it could be of benefit having certain sections consistently coloured (e.g. sections like method of administration or particular warnings and precautions to alert the patient's awareness).

Article 62 of Directive 2001/83/EC, as amended, also permits the use of images, pictograms and other graphics to improve comprehension except for elements of promotional nature. As detailed in the draft “readability guideline” the use of pictograms, symbols and graphics tends to be misleading and confusing due to cultural differences although it is judged as a very helpful tool for improving readability of package leaflets [111].

There have been some attempts in the past to test different pictograms for the reason of improving readability of package leaflets, but have not been successful due to cultural differences in the understanding and especially misunderstanding of the symbols (e.g. a slashed belly of a pregnant woman was misinterpreted as avoiding pregnancy as opposed to its intended meaning, i.e. “do not use the medicinal product during pregnancy”). Nevertheless, it is deemed that possibilities remain to create pictograms and symbols especially with regard to the preparation and administration of different dosage forms. One example could be the correct demonstration of dissolving a dry powder of an antibiotic preparation with water, its storage and its processing immediately prior to administration including details on the time intervals for application, as it is a medicinal preparation which is widely used especially in paediatric populations. The same would be easily applicable for displaying certain storage conditions with regard to temperature control.

Since, however, the user consultation of package leaflets of different marketing authorisation holders with pictograms – even if the same pictograms would be used in the same context – will not necessarily lead to a consistent rating and understanding of the symbols, it seems worth to establish a separate guide by the European Commission with symbols that are acceptable and even more important unambiguous for the whole European Union. Particularly for the usage of pictograms, a balance between harmonisation across different language texts and insurance of common understanding is required. Such a common approach could be achieved in close collaboration with pharmaceutical companies, the European pharmaceutical associations and appropriate patient organisations.

3.7 Outlook and critical evaluation

It has been generally accepted for a number of years that the informed consent of a patient is a necessary condition for enrolling patients or healthy volunteers in clinical trials. The purpose of this informed consent process is that the patient is informed about the project in a way which makes it possible for him to understand what participation in the project entails. This information is given both in written and in oral form, although the extent of the oral information can be variable.

The situation is quite comparable to treatment of patients by their physician. The information on the therapy is also given verbally via the dialogue with the attending physician and additionally via the package leaflet of the respective medicinal product that was prescribed to him. It is well known that patients forget or misunderstand much of what is discussed during a consultation. One study showed that, on average, patients had forgotten half of what the doctor had told them within 5 minutes of leaving the consultation room [109]. Therefore, it can be argued that – in line with the informed consent for clinical trials – the giving of patient education materials in addition to verbal advice by the physician and / or pharmacist is of benefit for the safe use of medicinal products.

The package leaflets, however, have been repeatedly criticised for the complexity of their content resulting in patients which are not adequately informed on the safe and adequate use of the medicine in question. Criticism is levelled in particular at the graphic design, the wording and its medical / pharmaceutical technology and especially the confusion or over-burdening of patients with the volume of information presented. The latter is not surprising in so far as an incorrect or even missing package leaflet presents a severe matter of liability for the marketing authorisation holder (see section 3.1.1.1 *Purpose of package leaflets and liability aspects*). In order to prevent any event of damage, pharmaceutical companies are obliged to present any scientific expertise and research data according to the current status.

With the revision of the European Directive 2001/83/EC and the current draft “readability guideline” a number of these weaknesses of the package leaflets with regard to readability and legibility have been addressed and additional requirements have been implemented to improve the situation. An important step towards refinement of the package leaflets has been made by the introduction of compulsory consultation of target patient groups and the description of the outcome as part of the marketing authorisation application.

The current draft version of the “readability guideline” gives support in how to design a package leaflet in order to ensure an optimum readability and also details in which way

user consultation may be performed by concentrating on the Australian method of a face-to-face interview with patients. The draft “readability guideline” may be assessed to be appropriate to improve the quality of package leaflets from a patient’s point of view. However, a number of suggestions as detailed in the guideline have to be judged to be both, rather improbable and unsuitable, from a practical point of view (e.g. print size and line spaces) whereas others are helpful tools for improving the legibility of package leaflets (e.g. use of an active style, avoidance of technical terms and inclusion of lay terms).

Apart from several items of the draft “readability guideline” which deserve revision and optimisation as detailed in the sections above, the most pressing and important topic should be the attempt to reach a common European understanding of the implementation of the “readability guideline” including performance and acceptability of user consultation methods. Especially concerning the increasing number of European marketing authorisation procedures a harmonised approach of all European member states is deemed vitally important to improve the planning reliability and controllability of application procedures, regardless whether it is a new marketing authorisation application, a variation application or a renewal. In fact, a crucial item is the lacking guidance and uncertainty in which situations a user testing will be required, e.g. which safety changes actually necessitate a user testing whereas others not. The same applies to the acceptability of bridging reports and their prerequisites as well as waivers for user testing.

Furthermore, it is strongly suggested to implement and validate an alternative testing method that makes it possible to avoid a complete user test if only single sections of a package leaflet are changed as part of a variation. In addition, the expression “significant changes” in the scope of a variation is yet to be fully defined. Critical safety issues and the degree of consideration in patient consultation will need to be defined upfront to enable companies to judge ad hoc whether user testing will be dispensable. In case of uncertainty pharmaceutical companies are asked to decide in favour of patients’ interests and conduct patient consultations.

According to the draft “readability guideline” the target patient consultation must not necessarily be the interview technique according to the Australian method but different approaches are acceptable as long as these are appropriate forms of consultation. However, currently no further alternative method recognised EU-wide is mentioned in the draft “readability guideline”. The criteria for appropriate and adequate conduct of other performance-based methods are yet to be clearly defined as it is not acceptable from an applicant’s point of view that competent authorities will judge applications on a case-by-case basis. As long as there are no common acceptance criteria for user testing available on a European level, marketing authorisation holders will tend to stick to the

“conservative” approach of user testing according to the Australian method in order not to endanger their regulatory activities and the respective timelines behind. Appropriate clarification is therefore highly appreciated.

In fact, although the Directive 2001/83/EC, as amended, is in place since 1.5 years, there is still room for discussion and interpretation of the requirements of user testing for both – pharmaceutical industry and competent authorities. In order to implement more reliable and definite general conditions, it has to be ensured that the guidance and its implementation is binding for all member states involved. Currently provision of services by CROs is especially difficult due to varying interpretations, implementation and assessment of guidelines by all parties involved and especially by different national authorities. Although it is welcomed that strict rules are avoided within the current draft “readability guideline”, it is still unclear in how far authorities will nevertheless insist strictly on the recommendations of the guideline. A flexible approach of the interpretation and application of the guideline is appreciated while also having a more reliable prediction of the expectations of the authorities.

Summing up, it can be concluded that competent authorities undertake rather inconsistent interpretations of the current requirements with regard to e.g. definition of target groups, pass-criteria and definition of key safety messages, resulting in ambiguous demands for the pharmaceutical companies and the CROs offering services in the field of user testing. Furthermore, with the revision of the existing “readability guideline” the requirements have been tightened, e.g. successful passing of the user test has become much more difficult, printed full colour mock-ups are specified for user testing as opposed to specimen etc. Apart from others, criteria for exemption of user tests and for repetition of user tests, where needed, are missing, which also applies to the acceptability of alternative methods for user testing and the optimum time point for performing the user tests.

Consequently, further experience with the applicability of the draft guideline and its interpretation is necessary in order to finally develop guidance for both, applicants in industry and assessors involved in the assessment of user consultations. A first summary of a survey conducted in the United Kingdom has been published just recently, detailing a number of points to consider in the context of issuing consumer-friendly package leaflets [105].

Such a common approach and understanding on European level is especially important with regard to multimorbid patients which depend on using a couple of different medicinal products at the same time. According to the differences in understanding and definition of requirements of the various European member states, it is not too unlikely

that different package leaflets – although all being user tested – will show differences and will most likely cause confusion. This is particularly awkward as a huge number of multimorbid patients are elder patients which per se are likely to have difficulties on handling package leaflets and concentrating on their contents.

A further perspective recommended for future evaluations in the scope of user testing is an investigation in how far consultation with target patient groups may be replaced by expert ratings – at least to some extent. Quite a number of surveys have been performed on this topic indicating a significant correlation between the expert and patient examinations of the content of the package leaflets. The authors of different studies performed in Sweden on package leaflets from common medicinal products concluded that package leaflets that score above average on the expert examination of content (with regard to adherence to the European Directive 92/27/EEC [58]) will also score above the average on the patient examination [112, 113]. In fact, the performance of routine examinations of leaflets that could be limited to some extent to tests by experts would be of particular benefit for pharmaceutical companies to reduce the number of patient consultation tests (see section 3.2 *Consultation with target patient groups by interview technique based on the “Australian method”*). Of course, such an approach will necessarily require further evaluation and validation to verify an existing correlation between the expert and the patient’s scoring.

Improving the readability and legibility of package leaflets may also be achieved by enhancing the general acceptance of package leaflets by consumers by help of giving details on the benefit of the respective medicinal product. It has already been proposed by the British Committee on Safety of Medicines that additional “benefit” information would be most helpful for prescription medicines and, in particular, preventative or long-term treatments [73]. Currently, the section “What is your medicine and how does it work” includes information on the pharmacotherapeutic group to which the product belongs and the indication only. However, including additional information about the benefits of taking the medicine and some background information might turn out advantageous. It has been suggested to include a few sentences detailing why it is important to treat the disease and what the likely clinical outcome would be if the disease remained untreated, whether the medicine is being used to treat the underlying disease (curative only) or for control of symptoms etc.

In fact, it has always been criticised that package leaflets can be alarming to medicine users due to the fact that they mainly deal with possible side effects and other warnings which are required according to European drug law. Inclusion of information about the potential benefit of the medicine in order to provide balance and context when considering risks associated with the respective medicinal product is worth to be

examined for improvement of package leaflets. Nevertheless, any such additional information – although being for the benefit of the readability of the package leaflet – should be restricted to a meaningful extent in order not to unnecessarily expand the information presented in package leaflets which is probably counterproductive and limits comprehension. In addition, any advertising character of such a section in the package leaflet has to be clearly prevented.

The American FDA even goes further and has implemented a new section called “highlights” for prescription drugs to provide immediate access to the most important prescribing information about benefits and risks [114]. This summary outlining the most important information about a product, including drug safety and benefits, is prominently displayed at the top of the page. It includes a section “recent major changes” which is a list of all substantive changes made within the past year to the following sections of the prescribing information: “Boxed Warning”, “Indications and Usage”, “Dosage and Administration”, “Contraindications” and “Warnings and Precautions” [115]. In fact, as described above, additional information may not necessarily be of help for improving the readability and / or legibility of package leaflets. Although this proposal has been made for Europe also, it remains doubtful whether this index of changes is of real help for the patient or whether it is a source of further confusion only as the patient, especially the one who uses the medicine for the first time, might get lost with such an arrangement.

Apart from the recommendations and requirements which information has to be stated in the package leaflet and in which order, a crucial point remains the style and syntax of package leaflets (see section 3.6.5 *Syntax*). As detailed above, the outcome of different surveys concerning the style and complexity evokes controversy whether subjects having completed high school or beyond will actually not mind if package leaflets are written oversimplified [116].

In fact, it seems more appropriate to make patients get familiarised with package leaflets, their contents and structure in general. Intensification of the exchange of information during the consultation with the attending physician would surely be of benefit for improving the understanding at the patient’s side. The same applies to the counselling interview in the pharmacy including the authoritative recommendation of the pharmacist to read the package leaflet after having pointed out important points.

In addition, it seems adequate to consider improved health education at school to improve the knowledge and acceptance of a healthy way of living including training in reading and understanding package leaflets. Such an attempt has even been proposed in Great Britain some years ago [117].

In Article 21 (3) of the European Directive 2004/27/EC, amending Directive 2001/83/EC, it is detailed “*The competent authorities shall make publicly available without delay the marketing authorisation together with the summary of the product characteristics for each medicinal product which they have authorised.*” [1]. In this way, the scientific assessment of quality, safety and efficacy of medicinal products authorised to be placed on the market in the European community is made publicly available to any interested parties [118]. In fact, this leads to the critical questions whether the Summary of Product Characteristics, which is addressed to health care professionals only by intention, will require consultation with target patient groups as well due to the fact that the SmPC will be publicly available as part of the transparency initiative. If this would actually be deemed applicable, the meaning and use of the SmPC would be distorted. Therefore, it is highly recommended to detail in an appropriate European guidance that user testing of the SmPC is not intended or covered by existing guidance.

A further item that requires careful consideration are alternative offers for providing health information to patients. With regard to Germany, the “Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen” (IQWiG) started with its internet portal on 07.02.2006 to provide independent, objective and certified information for the patients. According to an evaluation of Fuchs the information provided to the patients does not only lack adequate depth and correctness, but is insufficient concerning the testing for readability of the content also [119]. It should be expected that the same requirements apply – at least in principle – to patient information provided by such an institution as it is asked for by the competent authorities in case of package leaflets for medicinal products.

In any case, it has to be kept in mind that all measures required by the European Directive and the subsequent further guidance documents will not be able to produce package leaflets which will serve the necessities and requirements of both, pharmaceutical companies and health authorities and the consumers on the other hand. The design and content of package leaflets will always have to present a balance between the liability issues of the marketing authorisation holder and the justified desire of the consumers to be informed in depth, which necessarily implies comprehensive texts that may be deterring with regard to the safety information. This dilemma is most unlikely to be resolved and ongoing discussions concerning this topic are to be expected for the future also.

4 SUMMARY

Within the framework of the revision of the European Drug Law as part of the European Directive 2004/27/EC major changes have been implemented in terms of the rules on packaging in order to ensure the proper use of medicinal products. These innovations include Braille requirements for labelling and the package leaflet to address the particular needs of blind and partially-sighted patients. Further on the compulsory consultation with target patient groups for package leaflets has been newly introduced.

Although there is no doubt about the justified request of blind and partially-sighted patients for self-determined information on medicinal products and the respective package leaflets, it should not be forgotten that meeting these requirements is associated with enormous efforts by the pharmaceutical industry. For demonstration purposes the implications for establishing Braille labelling on secondary packaging materials as well as for creating package leaflets suitable for blind and partially-sighted patients are detailed. Particular difficulties with regard to nationally different special characters in Braille for the European languages and the challenges concerning Braille labelling for multilingual packaging are pointed out. Emphasis is placed on the demanding technical aspects for Braille on folding cartons and the respective implications for the workflow within pharmaceutical companies. In addition, different approaches of some European member states with regard to package leaflets being suitable for blind and partially-sighted patients are described.

The second part of the present thesis deals with the recently implemented obligatory consultation with target patient groups for package leaflets. Patient information leaflets have always given reason for discomfort as they are judged as being too difficult and incomprehensible or even misleading and unsettling. Checking the legibility and comprehensibility of package leaflets by user testing has been established as a means to ensure the appropriateness of the contents and appearance of the leaflets. The different approaches for performing such a user testing are detailed including an illustration of weak points and disadvantages of the various test methods. Fields for further improvement of package leaflets and the respective user test procedures are figured out and discussed including proposals for sound justifications for waivers and bridging reports in certain situations as opposed to entire user testing.

Both, Braille labelling and user testing, are undoubtedly meaningful and beneficial measures for improving the safe use of medicinal products. The current regulatory requirements, however, do provide room for further improvement and clarification especially in terms of harmonisation of requirements on a European level – to serve the well-being of the patients and the feasibility of the pharmaceutical companies.

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6 APPENDICES

Appendix 1: Status of Implementation of Braille requirements and availability of package leaflets for blind and partially-sighted patients at member state level, status as per 13 March 2007 [120]¹³

EU member state	Member Associations feedback on the national situation	
Austria	Status of national implementation	Draft application decree for labelling, SmPC and package leaflet expected by 2007. Final decree should refer to the annotated QRD-template, Rev. 7. Name + strength to be mentioned. Required type of Braille: Marburg Medium
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 02.01.2006	Implementation deadline: 01.01.2011
	Enforcement for new products	Enforcement on 02.01.2006
	Exemptions	MAH may apply for exemptions on a case-by-case basis
	Leaflet for blind / partially-sighted	Should be available on request from patients' organisations; pragmatic approach by authorities
Belgium	Status of national implementation	Implemented via the Royal Decree of 14.12.2006. Name (and strength / pharmaceutical form if needed) to be included on the packaging. Recommendation: Marburg Medium (acceptance of "Code Antoine" by national patients' organisations, also)
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised or submitted before 01.01.2007	Implementation deadline no later than 5 years after enforcement date of the Royal Decree (as of 01.01.2007)
	Enforcement for new products	Compliance with Braille requirements for dossiers submitted as of 01.01.2007
	Exemptions	Medicinal products not delivered directly to the patient and administered by health care professionals only
	Leaflet for blind / partially-sighted	National authorities and patients' organisations are exploring possibility of a "centralised solution"; 5-year transition period for products authorised or submitted before 01.01.2007
Cyprus	Status of national implementation	Brand name (and strength if more than one) to be mentioned
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 30.10.2005	Braille is not required
	Products authorised after 30.10.2005	Braille provision mandatory

¹³ As Bulgaria and Romania have joined the European Union only recently as of 01.01.2007, the status of implementation is currently missing.

EU member state	Member Associations feedback on the national situation	
	Exemptions	Small packs, hospital packs and other products administered by health care professionals
	Leaflet for blind / partially-sighted	On request from patient's organisations in formats appropriate for the blind and partially-sighted
Czech Republic	Status of national implementation	Not implemented yet
Denmark	Status of national implementation	Required type of Braille expected to be Marburg Medium
	Commission guidance	Requirements consistent with Commission guidance
	All products	All batches released after 30.10.2020 must include Braille on the package. Earlier implementation for specific products approved under a MRP or DCP can be required.
	Exemptions	Products administered by health care professionals only and hospital only products
	Leaflet for blind / partially-sighted	Most of the leaflets available on website www.lmk.dk (i.e. product index on all marketed products)
Estonia	Status of national implementation	Brand name (and strength if needed) on the outer package; required type of Braille is Marburg Medium
	Commission guidance	Requirements consistent with Commission guidance
	Enforcement for new products	To comply as of 30.10.2005
	Exemptions	Products administered by health care professionals and in hospitals
	Leaflet for blind / partially-sighted	SmPC and PIL in audio format and Braille to be provided on patients' organisation request. PILs available on MAH's website as from 30.10.2005
Finland	Status of national implementation	Name (and strength if needed) on the outer package. Type of Braille letter not specified in national regulation.
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised or submitted before 30.10.2005	All batches release after 30.10.2005 must include Braille
	Enforcement for new products	Braille requirements applicable for products submitted after 30.10.2005
	Exemptions	Hospital packs and other products administered by health care professionals
	Leaflet for blind / partially-sighted	The Finnish association (PIF) owns a national pharmaceuticals compendium database, in which a new part has been created with support of the Finnish agency to include patient leaflets by the pharmaceutical companies. Database will be publicly accessible as of April 2007 with possibilities of using large print and audio.
France	Status of national implementation	Name (and the strength if more than one). Flexibility regarding type of Braille, but specific Code "Code Antoine" mandatory.

EU member state	Member Associations feedback on the national situation	
	Commission guidance	Requirements should be consistent with Commission guidance
	Products authorised before 30.10.2005	Transition period expected to be 3 years, to be confirmed via a decree
	Exemptions	Products administered by health care professionals
	Translation in Braille	Usually "Handicap zero", an association for the blind and partially-sighted located in France, asked for translating documents
	Leaflet for blind / partially-sighted	Not yet finally decided. Currently under discussion whether package leaflet is made available also on request from patients.
Germany	Status of national implementation	Implementation completed on 26.04.2005. Required type of Braille is Marburg Medium.
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 30.10.2005	Implementation deadline is 30.10.2007 for all products authorised or renewed before 30.10.2005
	Exemptions	For small batches
	Leaflet for blind / partially-sighted	No specific solution required as per national legislation. Currently, pharmaceutical associations discuss with the German association for blind and partially-sighted (DBSV) a project on the basis of the German drug compendium "Rote Liste" with the possibility for printouts in large characters or to generate automatic audio-versions.
Greece	Status of national implementation	Name, strength and active ingredients. Type of Braille is Marburg Medium.
	Products authorised before 30.10.2005	All medicinal products will need to comply no later than 31.12.2007.
	Enforcement for new products	Braille requirement immediately applicable for products approved as of 30.10.2005
	Leaflet for blind / partially-sighted	Should be available in audio (CD or tape) on request of patients' organisation
Hungary	Status of national implementation	Provision enforced on 30.10.2005. Type of Braille is Marburg Medium with special Hungarian characters.
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 30.10.2005	Not mandatory before end 2010
	Enforcement for new products	Braille requirements applicable for products authorised as of 30.10.2005
	Leaflet for blind / partially-sighted	Mandatory for all products. Agency develops a website that will present audible versions for all patient leaflets.
Ireland	Status of national implementation	Final legislation not yet available
	Commission guidance	Requirements are expected to be consistent with Commission guidance

EU member state	Member Associations feedback on the national situation	
	Products authorised before 30.10.2005	All medicines will presumably need to comply no later than 30.10.2010.
	Enforcement for new products	Braille requirements will apply for MRP and DCP submissions as of 30.10.2005. Applicable for national applications after the legislation enforcement date (anticipated some time after 6 th June 2007).
	Exemptions	Products intended for administration by healthcare professionals only
	Leaflet for blind / partially-sighted	Discussions ongoing. Applicable for applications made after the legislation enforcement date according to the draft legislation.
	Readability testing / Quality control for Braille	Not required but the Irish agency is implementing the quality control provision by requiring a declaration of compliance to be submitted with applications and by marketing compliance monitoring (see http://www.imb.ie/uploads/publications/1856107_Braille%20website%20guidance.doc).
Italy	Status of national implementation	Name in Braille required since 1998 for reimbursable products. New text requires name, strength, pharmaceutical form and other relevant information in Braille for all medicinal products.
	Commission guidance	Reference to the Commission guidance given in the new text
	Exemptions	Products only intended for prescription by specialists and administration in hospitals
	Leaflet for blind / partially-sighted	Literal transposition of the Directive
Latvia	Status of national implementation	Name, strength (if more than one strength registered) on the outer packaging or on the inner if there is no outer
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 30.10.2005	Compliance with requirements by 01.01.2012. Leaflet for blind and partially-sighted be available by 01.01.2007.
	Exemptions	Products administered in healthcare institutions by healthcare professionals
	Leaflet for blind / partially-sighted	Leaflets should be provided on request in audio format
Lithuania	Status of national implementation	Implementing rules not yet available. However, companies have to comply with the Braille requirements of the European legislation.
	Commission guidance	Requirements should be consistent with Commission guidance
	Exemptions	Under discussion
	Leaflet for blind / partially-sighted	Not yet defined. Pharmaceutical industries and the blind associations will work closely to develop a pragmatic system.

EU member state	Member Associations feedback on the national situation	
Luxembourg	Status of national implementation	Literal transposition of the Directive
Malta	Status of national implementation	Fully implemented, however, only few patients in Malta are able to read Braille
	Commission guidance	Requirements consistent with Commission guidance
	Exemptions	Not required for vaccines
	Leaflet for blind / partially-sighted	Leaflet to be provided in a suitable format on request of the relevant associations and the patients
The Netherlands	Status of national implementation	Currently under discussion. Proposal: name and strength (if more than one strength)
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 30.10.2005	Draft national law does not explicitly state that requirements apply to products authorised after 30.10.2005 only
	Leaflet for blind / partially-sighted	Different options under discussion. One national telephone number with several options for getting information in different ways (leaflet read by speech-synthesizer, large-size font leaflet etc.)
Norway	Status of national implementation	Exact wording of Directive implemented in draft Regulation. Required type of Braille is Marburg Medium.
	Commission guidance	Minimum requirements from Commission guidelines with regards to labelling most likely to be followed. No marketing authorisations should be delayed because of Braille.
	Products authorised before 30.10.2005	Manufactured products will most likely need to comply no later than 2 years after implementation of the new legislation in Norway, most likely 2 nd half of 2008.
	Enforcement for new products	Manufactured products will most likely need to comply no later than 2 years after implementation of the new legislation in Norway, most likely 2 nd half of 2008.
	Leaflet for blind / partially-sighted	Norwegian pharma association works to establish digital reading on its website. Package leaflets will then be available in audio for blind and partially-sighted either by entering a computer or using a phone portal.
Poland	Status of national implementation	Implemented in draft Medicines Act
	Commission guidance	Requirements should be consistent with Commission guidance
	Products authorised before enforcement of the new Act	Products need to comply no later than 31.12.2009
	Enforcement for new products	Braille requirement will be applicable for products approved after enforcement date of the new Act. Nevertheless, a transition period is set up and products will need to comply no later than 31.12.2009.
	Exemptions	Exemptions for hospital products

EU member state	Member Associations feedback on the national situation	
	Leaflet for blind / partially-sighted	Leaflets should be available in appropriate format on request of patients' organisations
Portugal	Status of national implementation	Braille requirement applies for all products submitted after enforcement date of the new legislation, i.e. 31.08.2006
	Products authorised before the national legislation enforcement date	Transition period and measures yet to be provided by the Portuguese Health Authority
Slovakia	Status of national implementation	Enforced on 01.06.2006
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 01.06.2006	Implementation deadline will be 01.06.2011, i.e. 5-year transition period
	Enforcement for new products	All products for which application for marketing authorisation has been filed after 01.06.2006, must comply with Braille requirements.
Slovenia	Status of national implementation	Enforced as of 08.04.2006. Minimal requirements only: only the trade name on the secondary packaging should be in Braille (no strength and/or pharmaceutical form will be required in Braille in case the product is authorised in several strengths and/or pharmaceutical forms). Required type of Braille is Marburg Medium.
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised / filed before 08.04.2006	Transition period of 5 years from enforcement of the new national law is planned
	Enforcement for new products	Concerns all new products authorised after 08.04.2006
	Exemptions	Products administered by healthcare professionals
Spain	Status of national implementation	The new medicines law includes a very general statement on Braille.
	Commission guidance	Requirements will be consistent with Commission guidance according to the draft Decree.
	Products authorised before 30.10.2005	Will need to comply as of 28.01.2007
	Products submitted from 01.12.2005	Need to comply as of 28.01.2006
	Exemptions	Products intended for administration by healthcare professionals only according to the draft Decree
	Leaflet for blind / partially-sighted	Leaflet should be made available on request from patients' organisations only according to the draft Decree
Sweden	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 30.10.2005	Requirements are valid from 01.12.2005. A transition period of 5 years is envisaged (e.g. Braille on the packs at the latest 5 years after the latest approval date). However, for products authorised between 01.12.2000 and 30.11.2001, the new requirements shall be fulfilled by

EU member state	Member Associations feedback on the national situation	
		01.06.2006.
	Enforcement for new products	For products submitted before 01.12.2005, the old legislation will apply. For products submitted after 01.12.2005, the new legislation will apply.
	Exemptions	As detailed in the Commission guidance
	Leaflet for blind / partially-sighted	A website (www.fass.se) has been created years ago by the pharmaceutical industry: it discloses electronic versions of all existing patient leaflets and product information. The text can also be read by a synthetic voice. A system has been set up so that companies or the pharmacy (at time of dispensing) can order a leaflet with Braille to be printed out and sent by post to the patient. The project runs together with the patient organisation for the blind and visually impaired.
United Kingdom	Status of national implementation	The agency has prepared additional Q+As on Braille implementation. Required type of Braille is Marburg Medium.
	Commission guidance	Requirements consistent with Commission guidance
	Products authorised before 30.10.2005	Implementation of a 5-year transition period
	Enforcement for new products	Enforcement will concern all new products authorised after 30.10.2005
	Leaflet for blind / partially-sighted	A combined solution of some industry trade associations including a provider for the electronic system and the national blind associations has been worked out, the so-called X-PIL, which has been launched beginning of November 2006. It includes a single national phone number to request leaflets in audio, Braille or large print and is supported / promoted by pharmacists and the NHS.

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

Frankfurt, den _____
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