

Importance of Package Insert Information in the European Union

Medicinal and pharmaceutical experts questioning results

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Summary

Despite the multiplicity of optimizations already accomplished, package inserts frequently used by patients to obtain information relating to the medicine, are consistently met with criticism. In addition to poor readability and comprehensibility, confidence in using the medicine is reportedly diminished after reading the package insert. More appropriate package inserts for medicines which are available in the European Union, should have been achieved since the end of 2005, using readability tests. However for meticulous testing, it is vital that the opinions and experiences of patients, as well as specialists are included.

Actions to address these points are absolutely necessary to optimize therapy success and ensure safe medicine practice.

In 2005, four years after the accomplished patient study, a similar technique was applied to question 219 medical and pharmaceutical specialists in Jena

(Germany) and its vicinity. This related to the importance of different information in package inserts as well as requests concerning the structure sequence, text extent and content.

Analogue to patient study results, the information relating to “areas of application”, “dosage instruction”, “interactions” and “side effects” is “very important” to specialists. According to their opinions, this information should have priority on the package insert whilst “less important” content such as pharmaceutical companies, should be placed at the end. Apart from minor differences, specialists statements conform with patient requests.

In addition both groups requested more concise patient information, limited to the most important information. The specialists reported that patients frequently have less confidence using their medicine after they have read the package insert.

Considering the results of this study, it could be stated that the package insert sequence struc-

ture which was converted in Autumn 2005 better meets the desires of specialists and patients than the previous version. However, the following points must be strongly considered in the future, whereby an examination of the existing legal bases is also necessary.

1. Reduce the text extent to substantial text only.
2. Take action to ensure that patients are not inclined to act non-compliantly after reading the package insert.

Zusammenfassung

Die von den Patienten zur Arzneimittelinformation häufig genutzten Packungsbeilagen stehen trotz einer Vielzahl bereits durchgeführter Optimierungen immer wieder in der Kritik. Neben der schlechten Lesbarkeit und Verständlichkeit wird auch über ein gesunkenes Vertrauen berichtet, das Arzneimittel nach dem Lesen der Packungsbeilage anzuwenden. Hinsichtlich patientengerechterer Packungsbeilagen ist seit Ende

2005 für innerhalb der Europäischen Union vertriebene Arzneimittel die Durchführung eines Lesbarkeitstests verpflichtend. Damit diese Tests zielgerichtet durchgeführt werden können, sind neben den Meinungen und Erfahrungen der Patienten auch die der Fachkräfte von Interesse.

Im Jahr 2005, vier Jahre nach einer Patientenbefragung, wurden im gleichen Studiendesign 219 medizinische und pharmazeutische Fachkräfte in Jena (Germany) und Umgebung zur Bedeutung verschiedener Informationen der Packungsbeilagen, aber auch zu ihren Wünschen zur Reihenfolge der Gliederung, zum Textumfang und Inhalt befragt.

Analog wie Patienten sind dem Fachpersonal Informationen über

die „Anwendungsgebiete“, „Dosierungsanleitung“, „Gegenanzeigen“, „Wechselwirkungen“ und „Nebenwirkungen“ „sehr wichtig“. Diese sollen nach ihrer Meinung auch an vorderster Position in den Packungsbeilagen aufgeführt werden, „wenig wichtige“ Inhalte wie zum pharmazeutischen Unternehmen dagegen an hinterer Stelle. Bis auf wenige Differenzen ist diese Aussage der Fachkräfte mit den Patientenwünschen konform.

Zusätzlich wollen beide Personengruppen kürzere und auf das Wichtigste begrenzte Patienteninformationen. Die Fachkräfte berichteten, dass Patienten nach dem Lesen der Packungsbeilagen häufiger weniger Vertrauen besitzen, ihr Arzneimittel anzuwenden.

Unter Berücksichtigung der Ergebnisse dieser Befragung kann festgehalten werden, dass die ab Herbst 2005 in Packungsbeilagen umzusetzende Reihenfolge der Gliederung den Wünschen der Fachkräfte und Patienten stärker gerecht wird als deren vorherige Version. Jedoch müssen folgende Punkte in Packungsbeilagen zukünftig stärker berücksichtigt werden, wodurch auch eine Überprüfung der derzeit bestehenden gesetzlichen Grundlagen notwendig ist:

1. Den Textumfang auf das Wesentliche reduzieren.
2. Maßnahmen ergreifen, damit Patienten nach dem Lesen der Packungsbeilagen nicht zu Non-Compliance neigen.

Introduction

Since 1999 every medicine distributed within the European Union has been required to include a package insert [1]; these inserts are therefore, the most frequently used source of written information for patients [2, 3, 4].

Medicine users and their family members or other people taking care of them, should be enabled to independently inform themselves via these information leaflets and/or to also read up on the contents and instructions received from their doctor or pharmacist. To ensure package insert uniformity in each European Union member state, content and layout are determined mainly by the European guidelines and recommendations [5–9].

For example the QRD Group, a working group of the European Medicines Agency (EMA), provides instructions relating to content order and text passages in package inserts [5]. This ensures that dosage instruction or possible side effects are explained in the same position as an English, Spanish or German patient information leaflet.

Further recommendations were published by the European Commission in the “Guideline on the readability of the label and package leaflet of medicinal products for human use” of 29 September 1998 [6], which will be updated according to Directive 2001/83/EC as amended by Directive 2004/27/EC [7–9]. To ensure well designed and easy to read patient information it includes for example, instructions relating to font size, type and colour, paper type, design and layout, syntax and symbol and pictogram use.

According to Articles 59 (3) and 61 (1) of Directive 2001/83/EC as amended by Directive 2004/27/EC, new standards for package inserts are required [8, 9]. The modified Article 59 (3) states that user consultation is necessary in order to demonstrate the package insert readability and usefulness to patients. According to the “Guidance concerning consultations with target patient groups for the package leaflet” of May 2006 [10], the Australian model developed in the 1990’s [11] can be used for realization of

readability tests. In addition, other methods are accepted provided they ensure that patients can locate and understand the most important information and are able to act appropriately from it [10].

However, not all European Member states have implemented the new Directive 2004/27/EC requirements into their national laws yet. In the Czech Republic and France the transition is still under discussion, while Austria, Germany, Ireland, Italy and the United Kingdom have already implemented the new rules, but in different ways [12].

For example, in Germany, there is no regulation to perform a user test for medicinal products authorised before 6 September 2005. For medicines which were marketed before this date it is recommended to perform a package insert test whenever major changes in the package leaflet are expected, e.g. variations for new indications and renewals. 1 January 2009 is the implementation deadline for newly structured package leaflets.

The United Kingdom will require user consultation for applications

from 1 July 2005 and all leaflets should reflect readability testing by July 2008 [12].

Testing all available package inserts is not possible in such a short time frame. Thus, the new implementation requirement time allows the pharmaceutical companies and agencies to collect data from package insert information locatability and comprehensibility tests.

To achieve effective readability tests, knowledge relating to content importance for consumers and specialists must be applied, as well as the needs expressed for legible and easily comprehended texts.

This is based on various patient studies [3, 13] such as a study of 855 participants [14], accomplished in November 2001 in Jena (Germany) in which consumers stated as “very important” the “areas of application”, “dosage instruction”, “contraindications” and “possible side effects” [4].

In general, it cannot be assumed that medical and pharmaceutical specialists judge similarly to patients [15]. To develop a more appropriate package insert test and patient information, specialists were asked in this study, to strongly consider their opinions and experiences.

Study design

The questioning predominantly took place in medical surgeries, pharmacies and the local university clinic in March and April 2005 and was voluntary and without financial remuneration.

The questionnaire previously used in the patient study accomplished in Jena 2001 [14] was also used in this study. In addition to demographic data such as age and gender, specialists were meant to evaluate the importance of package insert paragraphs prescribed in the German Drug Law (AMG, Arzneimittelgesetz) § 11 with the help of a scale ranging from “unimportant”, “less important”, “important”, “very important” to “most important”.

Medical and pharmaceutical specialists were subsequently asked to

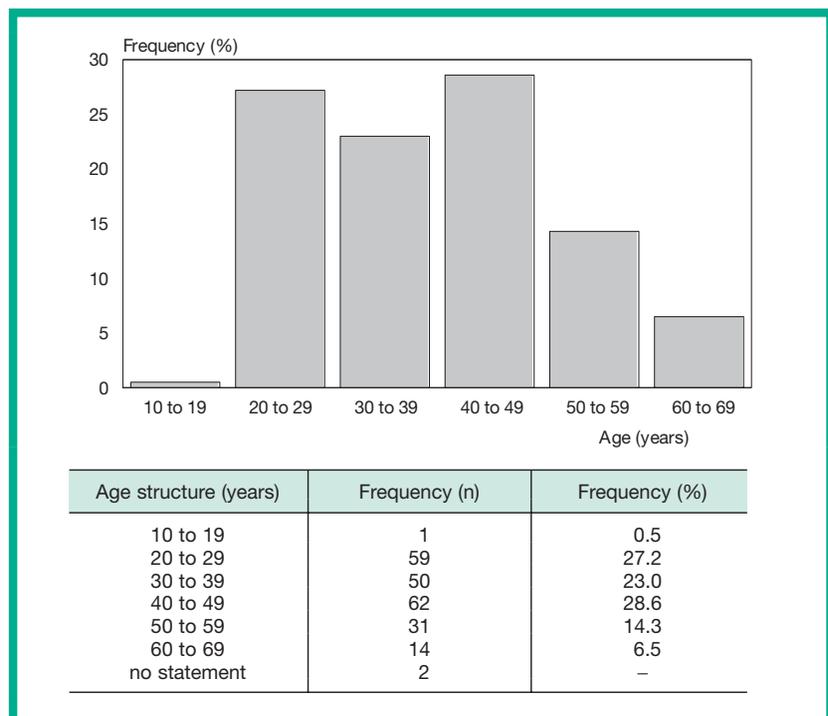


Fig. 1: Age structure of medical and pharmaceutical experts questioned (n = 217; two persons gave no statement).

state their desired information structure, evaluated preliminarily by assigning numbers 1 to 13, where the content most desired for first place received number 1.

A further evaluation also applied to text extent. Here, the specialists could express their opinion as to whether the package insert extent and content should “persist”, “be shorter” or “be larger”. Finally, each participant had to state one of the following, according to whether prior to application, they would normally read the medicines package insert: “never,” “sometimes” or “always”.

Each participant had the possibility to state their opinion of the package insert, in the concluding free-text field.

Biometric treatment

After coding the quantifiable data and accomplishing double data input to examine data record correctness, the respective medians for information importance and structure sequence were calculated.

Percentage fractions were determined for package insert extent and content requests, as well as frequency of reading and opinions noted in the free-text field.

Results

219 out of 300 questionnaires distributed were available for the evaluation, which corresponds to a return rate of 73 %. At the time of study the specialists were between 18 and 65 years of age, the average age was 40 years (Fig. 1).

Participants were predominantly women living in Jena (80.2 % each). The distribution of the education level illustrated a great number of specialists with a university degree: 10th class n = 61 (28.2 %), A-level n = 27 (12.5 %), technical college n = 25 (11.6 %), university n = 103 (47.7 %) and no statement n = 2.

Four specialist groups were questioned in total: practitioners n = 50 (23.0 %), other medical profession n = 57 (26.3 %), pharmacists n = 53 (24.4 %), other pharmaceutical profession n = 57 (26.3 %) and no statement n = 2.

Table 1: Frequencies of answers given by medical and pharmaceutical experts to the question “When you use a new medicine, do you read the package insert?”

Expert group	When you use a new medicine, do you read the package insert?		
	Never	Sometimes	Always
Practitioner	5 (10.0 %)	18 (36.0 %)	27 (54.0 %)
Other medical profession	0 (0.0 %)	26 (45.6 %)	31 (54.4 %)
Pharmacist	0 (0.0 %)	26 (49.1 %)	27 (50.9 %)
Other pharmaceutical profession	1 (1.8 %)	22 (38.6 %)	34 (59.6 %)
All	6 (2.8 %)	92 (42.4 %)	119 (54.8 %)

The question relating to whether or not participants read the package inserts if they themselves use a new medicine for the first time, was answered as follows: “always” by 54.8 %, “sometimes” by 42.4 % and only 2.8 % answered “never”.

Differences between the 4 occupational groups (Table 1), age groups and gender were minimal and always non significant. Nevertheless, 46.7 % of participants aged up to 29 years used the term “always” considerably less compared to people between 30 and 59 years (56.6 %) and over 60 years (71.4 %). 56.9 % of female specialists “always” read the package insert, both for their own medical use and to acquire information, contrary to the their male colleagues who represented 46.5 %.

Importance of different information in package inserts

After coding the opinions conveyed using 1 for “unimportant” to 5 for “most important” content and the following median calculations, it became apparent that medical and pharmaceutical specialists sorted the package insert information similarly to patients. According to their opinions, contents like “dosage instruction”, “therapeutic indications”, “contraindications”, and references to “interactions” and “possible side effects” were “very important”. They evaluated information relating to “ingredients”, “storage”, “application errors”, “therapeutic group” and “drug quantity” as “important”. However, specialists considered the package insert data relating to “Marketing Authoriza-

tion Holder and Manufacturer” and the “date of last update” as “less important” (Fig. 2).

Requested sequence of the structure

With very few exceptions, specialists’ requests relating to sequence

structure correlated with the importance of different package insert paragraphs, as stated. According to Fig. 2, specialists required the “very important” content to be placed at the beginning of the package insert, similarly to patients. The participants placed “less important” issues such as “Marketing Authorization Holder and Manufacturer” and “date of last update” at the end (Table 2). However, they stated that information relating to “ingredients” belonged in first place, even though it is not the most important content.

Important differences existed in specialists’ desired sequence structure and in how patients ranked “ingredients” and “therapeutic group” as well as the “precautions and special warnings”.

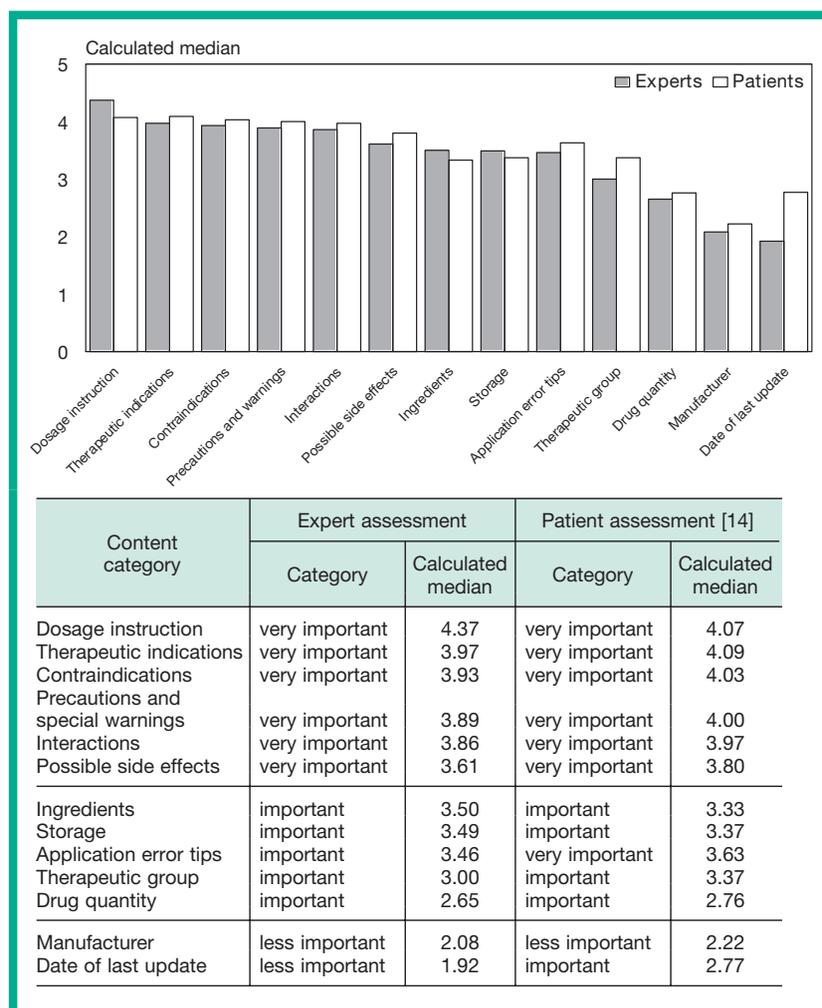


Fig. 2: Classification of information presented in package inserts through medical and pharmaceutical experts (n = 219) and patients (n = 855) [14]. Median categories: “most important” = 4.51 to 5.00, “very important” = 3.51 to 4.50, “important” = 2.51 to 3.50, “less important” = 1.51 to 2.50, “unimportant” = 1.00 to 1.50.

Table 2: Content category rank order in package inserts according to medical and pharmaceutical experts, the German drug law and patients.

Content category	Rank order in package inserts				Calculated medians	
	Experts	Patients [14]	After 14 th amend-ment of German drug law [21]	Before 14 th amend-ment of German drug law [27]	Experts	Patients [14]
Ingredients	1	3	10	1	1.64	5.12
Therapeutic indications	2	1	2	5	2.66	2.71
Dosage instruction	3	2	6	9	3.88	3.98
Therapeutic group	4	8	1	3	4.79	6.70
Contraindications	5	5	3	6	5.47	5.49
Precautions and special warnings	6	4	4	7	6.14	5.33
Interactions	7	6	5	8	6.51	5.94
Possible side effects	8	7	8	11	7.14	6.25
Application error tips	9	9	7	10	7.93	7.70
Drug quantity	10	10	11	2	9.83	9.56
Storage	11	11	9	12	10.07	10.12
Manufacturer	12	12	12	4	11.82	11.89
Date of last update	13	13	13	13	12.76	12.30

Package insert content and extent

Nearly every specialist favoured a more compact package insert in the future (87.7 %). Not one single participant chose to have more information than that already given (Fig. 3).

The evaluation concerning future package insert content was similar. 89.5 % wanted content limited to most important. In contrast to this, only one participant required a package insert with more detailed contents (Fig. 4).

As age increased, participants favoured shorter package inserts, limited to the most important information, however non-significantly (Table 3).

Further specialists' opinions on package insert

In addition 33 (15.1 %) out of 219 participants expressed their opinions in the free-text field at the end of the questionnaire, in which multiple comments were given. The lack of clarity and comprehensibility in the package insert was most frequently criticized. Nearly a third of participating specialists were of the opinion that package inserts unsettle patients and therefore have a negative affect on compliance and

the resulting success of the therapy (Table 4).

Other opinions and suggestions stated that information outlining tablet divisibility should always be contained in the package insert. Furthermore, specialists favoured simpler dosage instructions with a clearer emphasis on very important information, e.g. by using another font colour.

Discussion

In the European Union there are different forms of medicinal information available, package inserts and summaries of product characteristics (SmPC). The latter were only intended for specialist use and to make package inserts less difficult and more patient-oriented. In a German study of 430 doctors, accomplished by Mueller

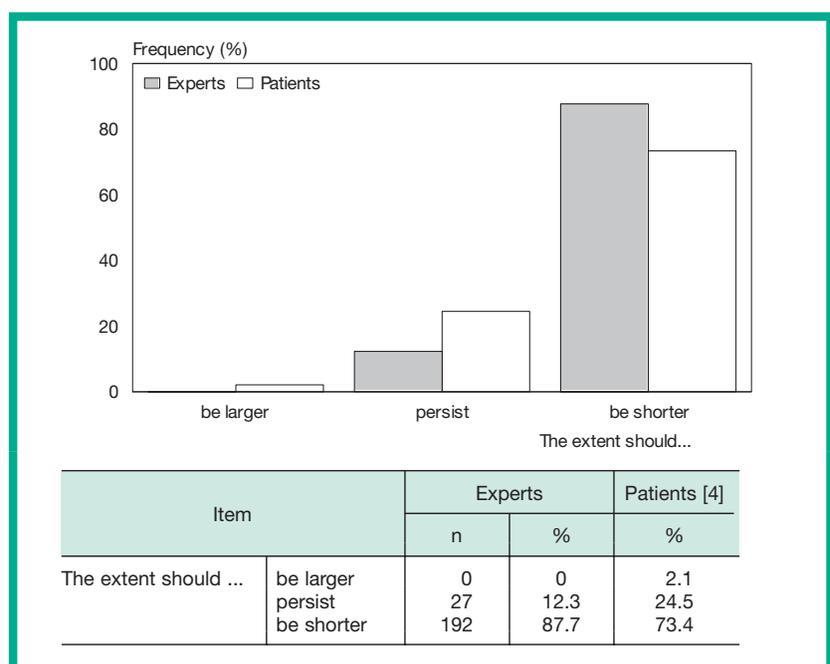


Fig. 3: Extent in future package inserts as requested by medical and pharmaceutical experts (n = 219) and patients (n = 821 / 822) [4].

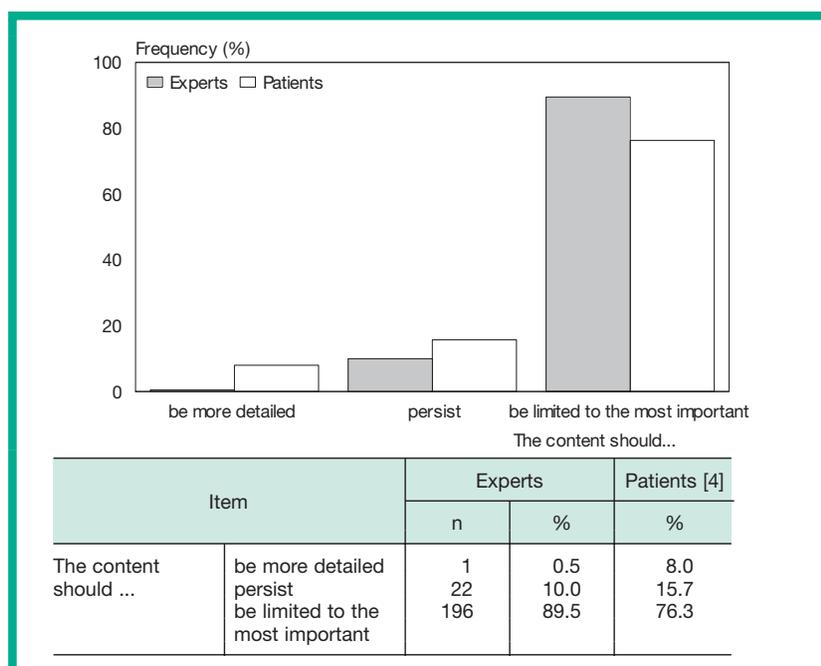


Fig. 4: Content in future package inserts as requested by medical and pharmaceutical experts (n = 219) and patients (n = 821 / 822) [4].

in August 2004, specialists used both information sources relatively frequently in the past, independently of the accomplished separation. In 10 presented information sources, the SmPC reached rank 4

and the package insert rank 6. This patient information was used by the medical profession more frequently than the original publications and other pharmaceutical company documentation [16].

Table 3: Extent and content in future package inserts as requested by medical and pharmaceutical experts, dependent on age (n = 217).

Age structure (years)	The extent should be shorter (%)	The content should be limited to the most important (%)	Frequency (n)
20 to 29	78.3	83.3	60
30 to 39	84.0	88.0	50
40 to 49	95.2	91.9	62
50 to 59	93.5	93.5	31
60 to 69	92.9	100.0	14

Table 4: Comments given by 33 experts and 197 patients [4] regarding package inserts (multiple answers were possible; 10 expert comments could not be classified).

Package inserts ...	Comments by 33 experts		Comments given by 197 patients [4]
	n	%	%
are not clear	10	30.3	11.7
are difficult to understand	9	27.3	51.8
make patients unsure	9	27.3	11.2
are unwieldy and too extensive	4	12.1	18.8
are difficult to read	4	12.1	14.7

Every second specialist “always” acquired information via package insert, whenever a new medicinal product was used. Presumably because package inserts are attached to each medicinal product, providing quick, simple information compared to SmPC. Specialists use this patient information almost as often as patients [14, 17, 18]. The differences between the 4 occupational groups were only slightly distinctive. However, similarly to patient studies [13, 19], female and older specialists used the package insert more frequently compared to the remaining participants.

What is important for the specialists?

In analogy to patient questionings [13, 14] specialists evaluated the information regarding “areas of application”, “dosage instruction”, “precautionary actions”, “interactions” and “side effects” as “very important”. Particularly more important for non-professionals was the package insert date of the last update. In Mullers study, similar results occurred when doctors were questioned regarding the importance of different SmPC information. Minor deviations in sequence prioritizing were possibly caused by the use of a slightly different questioning technique and different questions [16].

Results achieved here, relating to the importance of package insert information for specialists, are important for compiling patient information and implementing required readability tests [9]. Based on these results and considering also the results already accomplished in patient questionings, “very important” information can be tested more accurately with user-friendliness in mind. For example, the written readability test developed by Fuchs considers these results [20].

Is the prescribed structure acceptable?

In the sequence structure desired by specialists and patients, greater

differences only existed in “ingredients”, “therapeutic group” and “precautions and special warnings”.

Comparing the results of both studies in Table 2 with the legal requirements as stipulated in the 14th Amendment of German Drug Law [21] based on the European Directive 2004/27/EC [9], it is clear that the sequence structure meets the needs of specialists and patients significantly more than the initial valid version. The new structure corresponds largely to suggestions previously published by Fuchs et al. 2003, regarding sequence optimization considering patient desires as well as medicinal safety practices [14].

The positioning of the heading “ingredients” in the medicine information reveals an important discrepancy between the suggestions published in 2003 and the required sequence in the drug law currently valid. Analogue to specialists’ and patients’ desires, listing the complete composition at the beginning of each package insert should be considered, rather than listing the active substances only.

For didactical and medicinal safety reasons, the “contraindications” as well as the “precautions and special warnings” have to be placed before the “dosage instruction”, thus ensuring that patients do not use the medicine before reading this “very important” information. Therefore justifying the prescribed dosage instruction rank used at present.

Should package inserts contain more information?

Fig. 3 and 4 illustrate that specialists were more opinionated compared to patients, stating that text extent and content must be reduced to vital information only. Essentially, the specialists’ and patients’ desires mentioned must be strongly considered. As versions currently distributed in the pharmaceutical market have an average text extent of around 3 DIN-A4 pages in 8pt font size, with a tendency to increase [22].

It is incompatible that “less important” information such as the information relating to the “Manufacturer and Marketing Authorization Holder”, is still so overrated, particularly in the package inserts of medicinal products which have received central European approval (CP). These versions must contain the appropriate addresses of the local company representative in each European Union member state, and this can amount to as much as 25% of the package inserts text extent.

Nevertheless, in order to ensure and improve clarity, a coloured design emphasizing the core statements would have to be discussed. However, the Bernadini et al. [23] study showed that 66 % of patients questioned, associated colour emphasis with advertising, thus rejecting this. In contrast to this, studies according to Kienzl [24] and Fuchs [19] showed that patients were very much in favour of coloured elements in package inserts.

Specialists also criticized the font used in package inserts which was often much too small. This is a result of the European Commissions recommendation [6], to apply a minimum font size of only 8 pts. Even this 8 pt font is not converted in some package inserts [22]. However various studies prove that readability is improved when a font size of up to 11 pts is applied [23, 25]. Therefore, some of the September 2006 Draft Readability Guideline font size recommendations may be not suitable. While, suggestions of between 16 and 20 pt font sizes for visually impaired patients are more difficult for people without visible impairments, to read. They should therefore be excluded from the European Guideline [7].

Despite the European and national recommendation to design a simpler package insert, incorporating only user friendly words [6, 26], specialists still complained about the use of technical and foreign words, as they cause a significant amount of uncertainty in patients after they have read the package insert.

In addition, specialists insist on a more patient-comprehensible dosage instruction. In an analysis of package inserts by the German pharmaceutical market published in 2006, every fifth version examined contained the active substance dosage amount in milligrams instead of a unit more comprehensible to patients, such as the number of tablets [22].

Specialists also commented on the topic “side effects”. A substantial demand included, improving the explanation referring to the relevance of side effects for patients, considering their occurrence frequency. This was already adopted in the 1998 Readability Guideline [6]. However, specific numerical data is still unavailable in some package inserts, as this recommendation was not converted into national guidelines until 2002 [26].

According to the Directive 2001/83/EC article 1, side effects are classified as “serious” and “not serious” [8]. However, specialists were of the opinion that patient evaluations via the information provided in the package insert were insufficient. This resulted in uncertainty and decreased compliance.

In a study of 197 patients, 11.2 % stated that they had no confidence to use the medicine after they had read the package insert [4].

Taking action is absolutely necessary, as decreased compliance reduces therapy success. In addition, it is well-known that package inserts with condensed text are more appropriate for patients and can significantly increase the confidence in therapy as well as comprehensibility of information [19].

Conclusion

The results achieved should enrich the past initiative concerning more appropriate package inserts for patients, according to the pharmaceutical industry and the European and national medicine agencies.

In addition, the existing legal requirements should inevitably be improved. However, a change in legal regulations in Germany is only

possible by modifying the European Community code relating to medicinal products for human use 2001/83/EG [8] as well as other European recommendations such as those of the QRD-Group [5].

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