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Draft Statement:

2. Proclamation of the revised version regarding the recommendations for package insert design according to paragraph 11 of the German drug law for human pharmaceuticals.

(state of discussion 07.04.2006)

Via the Directive 2004/27/EC several changes regarding the package insert design were discharged, which concerned for example the new sequence of the arrangement and the accomplishment of readability tests. Above all the practical implementation of new requirements raised questions relating to the conversion consistency. Therefore, based on the experiences of PAINT-Consult as provider of readability tests in addition to package insert research for many years, a statement is delivered to the draft specified above in the following.

1. Package insert readability tests

Putting new recommendations in place for discussion, before implementation, is in principle positive as it facilitates the inclusion of useful suggestions from practical experiences. Thereby, the Federal Institute for Drugs and Medical Devices (BfArM) perception as contained in the draft is particularly interesting, as the frequently asked question relating to the readability test accomplishment, is addressed and/or answered here.

It is important to have a clear regulation which states whether or not a readability test must be accomplished or can be void. Included also should be, the extent to which a readability test relating to one drug is generally sufficient for different application forms of pharmaceuticals, whether there are exceptions and if so which ones.

According to Fuchs, the following issues must supplement the written readability test (2, 3):

- The test procedure must contain a comprehensibility evaluation based on proved quality criteria. The proving must takes place prior to patient testing.
- The tested group must cover a minimum 2 groups of 10 people, which is similar to the interview procedure of Sless and Wiseman (4).
- In addition to questions relating to content, different participant statements relating to the package insert usability must also be questioned.
- The written readability test was evaluated via several studies (2, 5, 6).

2. Improving package insert comprehensibility

Active patient requesting

The patient target group can be better achieved via active requesting. However, this kind of patient motivation must be used carefully, e.g. in headings or contents of particular importance only. When this medium is used too frequently, the reader will no longer notice it as the effect is minimised. For this reason and in an effort to minimise the extent of information, each point in chapter 2 („Do not take / use X“ and „Take special care with“) according to the new annex relating to the wording of package inserts (7), should not start with <if you> or <when you>.

Statements with preferably precise usage instructions

The information contained in the package insert can only be appropriately used by patients via precise instructions. Non quantifiable phrasings like ‘high dosage” or “recently applied” should be avoided. They do not enable the patient to clearly rate the importance of the information brokered. Thus, some people will understand “recently used” as a time period of up to about 3 days, while others may comprehend it as being 1 month or more (2).

Usually, non quantifiable phrasings can be conveyed more comprehensibly per statements in numbers (2). However, for some issues there are too few results which convey precise information to patients. Chapter 2 „<Taking> <Using> other medicines“ contains the following sentence:

„Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.“

In addition to being too extensive for a usage instruction, according to the Readability-Guideline of 1998, this sentence is longer than the recommended maximum length of 20 words per sentence (6). Furthermore it contains the described non quantifiable statement “recently taken”. However, this statement is specified in the QRD-Template Version 7 (9), in which each company is supposed to use this ambiguous phrasing based on the Template.

<u>Suggestion for an improved and above all shorter phrasing</u>:

“Inform your doctor or pharmacist if you have used the following medicines within the last 14 days.” (2)

According to the half-life period of the medicines contained under this chapter, a shorter or longer time period of “14 days” might be necessary.
The current QRD-Template must be optimized simultaneously, to ensure unitary writing within the European Union and avoid problems such as other European Union member state admission authorities disallowing German texts.

A further example of the Template non quantifiable phrasings concerns the statements relating to „older people“. Information relating to age range in years should be listed similarly to children, this can be interpreted differently by everyone.

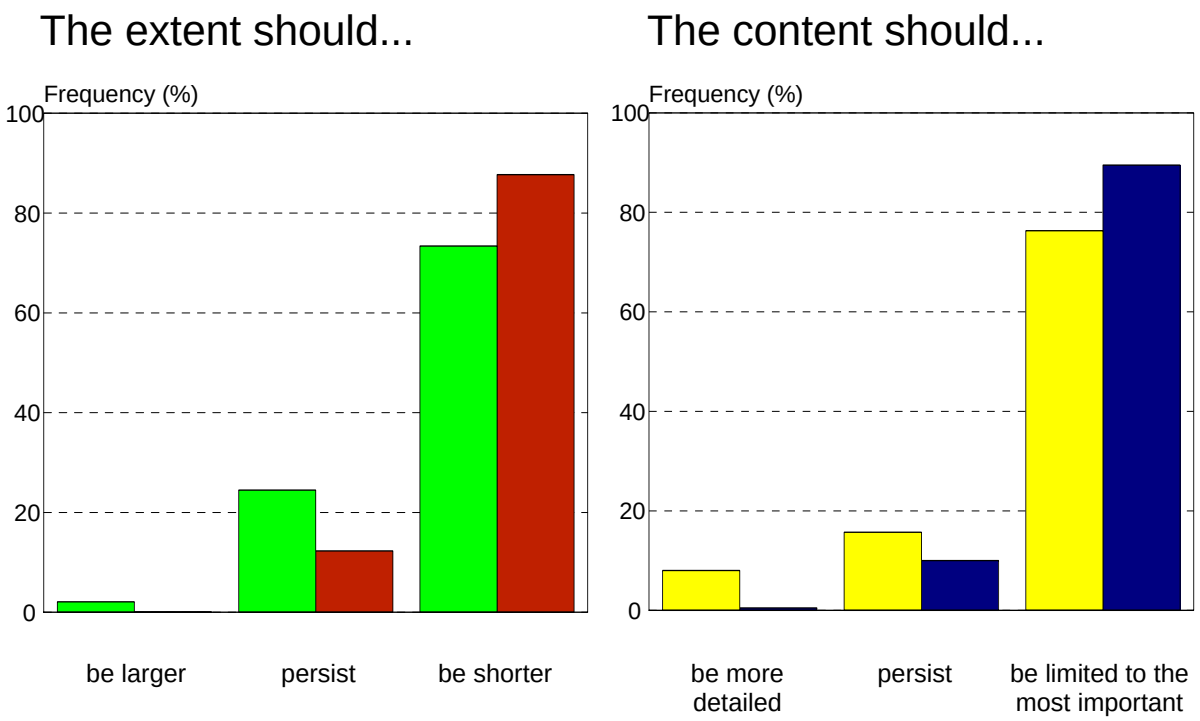
The heading „Take special care with X“ contains no precise usage instruction, the special precautionary actions to be accomplished are therefore not conveyed. A general reference to the doctor would surely be more significant: „Ask your doctor before you <take> <use> X“.

Many package inserts do not contain clear usage instructions under the subheadings „Pregnancy and breast-feeding“ and „Driving and using machines“, especially if there is an unclear data situation. For this reason more precise statements relating to these issues should be given such as:

- Do not use .../ Do not drive or use any tools or machines as
- You can use .../ You can drive or use any tools or machines after taking X.
- Ask your doctor or pharmacist for advice as to whether you can take this medicine during pregnancy or breast-feeding. / Ask your doctor or pharmacist for advice as to whether you can drive or use any machines during X therapy.

Renouncement of text repetitions

Text repetitions should be avoided where possible (8, 10) and should also be considered in the Templates. This is particularly important, since patients as well as medical and pharmaceutical specialists require shorter and more concise package inserts which are limited to the most important information (figure) (5, 6).



patients n = 855 (5), specialists n = 219 (6)

For example consulting a doctor or pharmacist as an action when side effects occur is recommended in the information box (below the name of the medicine) and twice within chapter 4. Given that this reference is of particular importance, it should be emphasized but listed only once. However, in addition to this, the National guidelines and QRD Templates must be optimized, particularly because the information box and chapter 4 states only "serious side effects". This non quantifiable phrasing does not ensure precise instruction usage.

Furthermore this chapter states the instruction to inform the doctor or pharmacist only if a side effect not stated in the package insert occurs. Based on this information alone, according to the extrapolation of PAINT1-study data (2); 900,000 people in Germany would only consult their doctor if a side effect, not mentioned in the package insert, occurred. This issue also represents a risk in drug safety.

Suggestion for shorter and more precise phrasing:

“Inform your doctor or pharmacist with each occurring side effect, even if this is not contained in the package insert.”

The Template contains a further repetition regarding the effective substance. This is specified under the name of the medicine and in chapter 6.

Expansion of content requirement for texts

The statement at the end of the proclamation, not to further expand the texts content requirement, is in principle to be welcomed. To facilitate the acquisition of each possibility, further and often very large texts are needed.

Here, all European and National template phrasing should be tested to evaluate whether or not they are necessary and/or if they can be more condensed. The extensive information box below the name of the medicine is to be taken as an example. In addition to the redundancy regarding the actions to take with side effects, already described above, the request to read the package insert is contained here. The text “Package leaflet - please read carefully”, in the past commonly used in Germany, was much shorter and originally better positioned i.e. before the name of the medicine in contrast to the current version. To convert the active request into a short phrase, it could be optimized as follows:

Suggestion:

“Please read the package insert carefully!”

The information in the package insert which relates to the Marketing Authorisation Holder and Manufacturer is of less importance to patients or the medicinal and pharmaceutical specialists (5, 6). However centrally certified medicinal package inserts contain the Marketing Authorisation Holder’s local representative from each European Union member country. This QRD Template guideline does not conform at all with patient requirement for short and most importantly, concise package inserts, already described above.

In addition to this, future package inserts containing the Marketing Authorisation Holder’s address only, should be discussed. Firstly, the additional Manufacturer’s address is of less importance to patients as well as medical and pharmaceutical specialists and secondly, it is not necessary for drug safety.

The recent specification of the Marketing Authorisation Holder’s European selling countries and the medicinal trade names is only an unnecessary increase in the package insert volume. Each pharmacist is able to state the appropriate names of the medicine or alternatives, based on internal software. These references should not be used in package inserts anymore.

Furthermore, although the 1998 Readability Guideline requires abbreviation avoidance (8), the abbreviation "EEA" is nevertheless used. In addition, this abbreviation is generally not well-known to patients. Examples of this ambiguous interpretation are as follows:

- **European Environment Agency;** under: www.eea.europa.eu/
- **European Energy Award;** under: http://www.eea.nrw.de/
- **European Economic Association;** under: http://ec.europa.eu/comm/external_relations/eea/index.htm
- **Einheitliche Europäische Akte;** under: http://de.wikipedia.org/wiki/EEA

Abbreviations

In addition to the abbreviation „EEA“ already addressed in chapter 6, other abbreviations relating to the composition of the medicine are also used in this chapter, such as the inactive substances E-numbers and their dispensatory related specifications such as, "Ph. Eur.".

Both are generally not comprehensible for patients. Substances with E-numbers are frequently classified by consumers as dangerous, even if they concern harmless substances such as saccharose.

Dosage instruction

The use of a table for the dosage instruction is reasonable. According to the PAINT1-study the clarity and comprehensibility of information can be increased in the process (2). In individual cases a well emphasized dosage instruction might also be easily understood without a table.

However, the body weight should generally not be noted in addition to the children age data. Since children do not always have their age appropriate weight (11, 12), a data differ related to the age and/of weight might occur.

A Paint-Consult study not yet published, was accomplished in May 2006 with 207 participants. The results found that dosage data concerning age and the body weight is of no assistance to patients in decision making. According to the results it is difficult for patients to seize the correct dosage via this form of dosage instruction.

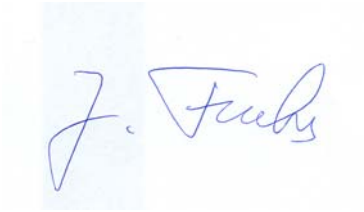
Therefore, for comprehensibility purposes only one criterion of choice should be recommended, either age or body weight. The data referring to the age should be preferred, as long as it does not concern a medicine with a small therapeutic index, such as cytostatic drugs.

Regarding the dosage instruction, the dosage stated in number of tablets or capsules and/or the volume of ready to use medicine should definitely be included in the QRD-Template. Unfortunately many package inserts contain dosage instructions in form of quantity specifications of the effective substance (13). According to the PAINT1-study such dosage references are very frequently misunderstood (2) (see abstract appendix 1).

Field of application

In relation to the chapter heading „What X is and what it is used for” the action mechanism should firstly be specified and only thereafter the actual indications should be listed. On account of this according to the PAINT1-study and previously accomplished readability tests, patients understand parts of the action mechanism as fields of application. For this reason a chapter heading sequence change is suggested, to allow the more important information relating to the fields of application to be specified firstly.

In addition to this, the heading should be written in more appropriate English, such as „What X is used for and what it is “. Several participants who had already accomplished a readability test, criticized the existing version of the heading.



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Appendix 1: PAINT1-study, a Cross-Over-Comprehensibility-Test of 5 original and 5 model package inserts [abstract] (2)

[Fuchs, J.; Hippius, M.; Schaefer, M.: Package inserts and their comprehensibility for patients. Proceedings Workshop Programme and Abstracts - 13th international social pharmacy workshop (2004) 42.]

Package inserts and their comprehensibility for patients

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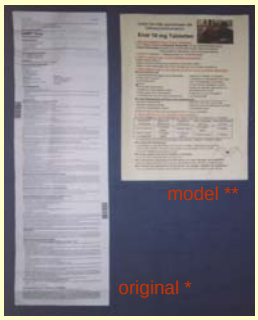
Background:
• Package inserts are very important for patient information
• Their suitability is still under discussion.
• Recommendations for testing the readability are given by the European Commission. [2]
• According to Sless and Wiseman: [1]
1. Over 90 % of the patients find the relevant information.
2. Over 90 % of those finding the information are able to understand it.
3. Thus over 81 % of the patients in total are able to use the package inserts appropriately.

Aims:
• The PAINT survey (package insert test) examined the comprehensibility and availability of information from five package inserts * for different drugs and five model package inserts ** for the same drugs developed for this test.

Methods:
• A questionnaire with 15 questions referring to the content of the package inserts was adapted using references by Sless and Wiseman [1], the EMEA [2] and the EFPIA [3] for a written survey.
• 1,150 patients were asked to participate in the PAINT survey.
• Cross over testing
• Every person got an original * and one model ** package insert within an interval of 4 weeks.
• Time: September 2002 to April 2003



Results:
• 1,105 persons answered the questionnaire in the first trial and 1,051 in the second trial (return rate: 95.9 and 91.2 %).
• Participants:
- 10 to 92 years old, average age: 38 years
- 69.1 % living in or near Jena, 30.9% in other parts of Germany
- 65.4 % woman, 34.6 % man
• Questions to the content of package inserts (Table 1)
- original versions: 74.7 to 85.8 % of all questions were answered correctly
3.8 to 6.9 % answers not found
- model versions: 92.6 to 94.4 % of all questions were answered correctly
2.2 to 2.5 % answers not found
• Time needed to answer the 15 questions (Table 2)
- original versions: 14.3 to 19.6 minutes
- model versions: 10.9 to 13.8 minutes
• The question: „What is the maximum dose for a day?“ (Table 3)
- original versions: 9.4 to 90.2 % answered correctly
0.9 to 9.9 % answers not found
- model versions: 83.6 to 94.0 % answered correctly
0 to 0.5 % answers not found
Frequently mistakes regarding the original package inserts were connected with dosage instructions in milligram instead of „tablet“ or volume. The maximal daily dosage was better found in those versions presenting this information in a table.

Conclusions:
• It is possible to improve package inserts.
• All models but only 2 original package inserts are easy to understand.
• With regard to dosage instructions the following is recommended:
1. Every dose should be given in a number of tablets or capsules and volume respectively.
2. Dosage instructions should be given in a table.

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PAINT
Package Insert Test

Table 1: Correctness of answers concerning the content of original vs model package inserts (15 questions)

package insert	correct answers (%) (calculated median)		answers not found (%) (calculated median)		n	
	original	model	original	model	original	model
Enalapril	78.5*	93.2	6.7*	2.5	218	214
Ibuprofen	85.8*	94.4	6.9*	2.3	215	213
Paracetamol	82.6*	93.3	3.8*	2.2	213	219
Repaglinide	79.0*	93.3	4.5*	2.3	214	216
Telmisartan	74.7*	92.6	6.2*	2.3	213	216

(* significant differences between the results of the original and the model version of package inserts)

Table 2: Calculated median of the time needed to answer the 15 questions

package insert	time to answer the 15 questions (min)		n	
	original	model	original	model
Enalapril	19.6*	13.1	203	197
Ibuprofen	18.8*	12.4	200	200
Paracetamol	14.3*	12.0	197	203
Repaglinide	15.3*	13.8	204	199
Telmisartan	15.3*	10.9	195	198

(* significant differences between the results of the original and the model version of package inserts)

Table 3: Calculated median for the answers to the question: “What is the maximum dose for one day?”

package insert	correct answers (%)		answers not found (%)		n	
	original	model	original	model	original	model
Enalapril	52.5*	83.6	0.9	0	217	213
Ibuprofen	90.2	90.0	1.4	0	215	210
Paracetamol	9.4*	84.9	7.0*	0	213	218
Repaglinide	36.0*	94.0	7.5*	0.5	214	216
Telmisartan	33.3*	92.1	9.9*	0.5	213	216

(* significant differences between the results of the original and the model version of package inserts)

Appendix 2: Questioning patients on the importance of different information as contained on package inserts and the desired sequence of the structure (n = 855 participants) (5)

A survey of package inserts use by patients

There are many problems associated with package inserts, according to a new study. As package inserts are one of the most frequently used sources of written information, approaches to optimise them should be explored

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There is an international trend to improve information for patients about drugs and therapy.[1,2] In 1993, at a meeting jointly organised by the WHO and the Council for International Organizations of Medical Sciences (CIOMS), the right of people to be informed about their healthcare was clearly defined.[3] Furthermore, patients are very interested to get more information and a greater say in questions regarding their own health. In 2002, a survey of over 8,000 people in eight European countries showed that 74% of the participants wanted to be more actively involved in treatment decisions.[4]

Both pharmacists and medical doctors can give verbal or written information to patients within or outside the hospital. The problem is that, by direct communication, only those who provide the information can estimate what each patient has understood. Health professionals, however, have limited time to convey comprehensive information. Therefore, there is a need for a combination of verbal and written information to increase knowledge and compliance.[5–7] This is in agreement with regulations issued by the European Parliament and the Council of the European Union Directive 2001/83/EC,[8] which requires that every drug has to have a package insert.[8,9]

So far, assessments of the package inserts of drugs by patients are rare, as are evaluations about their effects on patients' health. The survey described below attempted to assess the importance of different issues of package inserts from the patient's perspective.

Study design

A questionnaire focusing on expectations and preferences of patients regarding package inserts was distributed in November 2001 among 1,500 patients in a community pharmacy in Jena (Germany). Of these, 855 people answered the questionnaire (return rate: 57.0%; age: 13–89 years; average: 50 years; female: 66.2%). The educational training of the participants was as follows:

- Eight years: 18.9% (n=162); 10 years: 24.8% (n=212).
- A-levels: 8.1% (n=69); diploma from university for applied science: 17.8% (n=152); university: 23.5% (n=201); no statement: 6.9% (n=59).

The majority (79.6% of all volunteers) said that they "always" read the package inserts of newly prescribed drugs; 19.3% said that they did so "sometimes"; and only 1.1% said they "never" read them.

On request, participants classified the various subject matters of the package inserts into three out of five categories with regard to the importance for the patients. Information about "therapeutic indications", "dosage instruction", "contraindications" and "side-effects" were seen as "very important", whereas

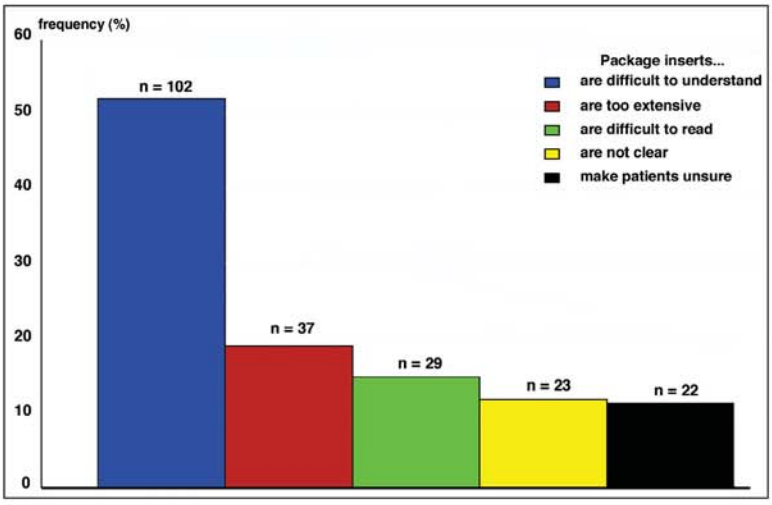

Figure 1. Selected comments about package inserts by 197 participants (multiple answers were possible; 57 comments could not be classified)

Table 1. Classification of the information presented in package inserts

Content category	Assessment by participants	Calculated median	n
Therapeutic indications	Very important	4.09	837
Dosage instruction	Very important	4.07	845
Contraindications	Very important	4.03	846
Appropriate precautions for use and special warning	Very important	4.00	849
Interactions	Very important	3.97	843
Possible adverse drug reactions	Very important	3.80	837
Hints for application errors	Very important	3.63	839
Storage	Important	3.37	844
Therapeutic group	Important	3.37	838
Ingredients	Important	3.33	838
Date of the last update	Important	2.77	846
Application form and quantity of the drug	Important	2.76	845
Manufacturer	Less important	2.22	846

Possible categories for assessment: "most important" – 5; "very important" – 4; "important" – 3; "less important" – 2; "unimportant" – 1

details about the "manufacturer" were considered as "less important" (see Table 1). This ranking is also reflected in the structure that participants suggested for future package inserts (see Table 2). This result was independent from the demographic variables of the survey participants.

The participants were also asked about their wishes regarding the amount of information given and the content for a future package insert. Out of 821 participants, 73.4% said they would prefer "less comprehensive" package inserts, 24.5% agreed with leaving the package insert as it was, and only 2.1%

Table 2. Rank order of content categories in package inserts according to patients and the AMG (German Drug Law),[17] in accordance with the Directive 2001/83/EC of the EU[1]

Calculated median	Content categories	Rank in the order of package inserts Patients	AMG §11
2.71	Therapeutic indications	1	5
3.98	Dosage instruction	2	9
5.12	Ingredients	3	1
5.33	Appropriate precautions for use and special warnings	4	7
5.49	Contraindications	5	6
5.94	Interactions	6	8
6.25	Possible adverse drug reactions	7	11
6.70	Therapeutic group	8	3
7.70	Hints for application errors	9	10
9.56	Application form and quantity of the drugs	10	2
10.12	Storage	11	12
11.89	Manufacturer	12	4
12.30	Date of the last update	13	13

wanted more information. According to 76.3% of 822 participants, a package insert should include "only the most important information"; 8% would have liked additional information; and 15.7% were satisfied with the content of the current package inserts. The size of package inserts was also criticised by 18.8%.

More than 50% of the 197 volunteers who gave comments about package inserts found it difficult to understand the information, and 11.2% felt insecure after reading the inserts (see Figure 1).

Discussion

The results of the survey show many problems associated with package inserts. As package inserts are one of the most frequently used sources of written drug information,[10,11] approaches to optimise them should be explored as soon as possible. This especially refers to difficulties in understanding the extensive information provided, and suggests a more suitable structure for package inserts.[12,13] Other studies confirm the results of this survey on the importance of the content and presentation of package inserts.[11,14,15]

Package inserts should contain only the information that is of importance for the patient, although this is debatable from a legal point of view. Another study, the PAINT survey,[16] showed that patients needed significantly more time to find the information they needed in the original versions of package inserts, compared with shorter versions. The address of the manufacturer for each Member State of the European Union is currently mentioned on package inserts, which can take up to 25% of the space available, and this might have to be reconsidered.[16]

Conclusion

According to the results of different surveys, the structure of package insert should be as follows, in order of importance:

- Name of the medicinal product.
- Ingredients.
- Therapeutic indication and therapeutic group.
- Contraindications.
- Appropriate precautions for use and special warnings.
- Dosage instruction.
- Hints for application errors.
- Interactions.
- Possible adverse drug reactions.
- Application form and quantity of the drug.
- Storage.
- Manufacturer.
- Date of the last update of the package insert.

The European Parliament and the Council of the European Union changed the structure of package insert with the Directive 2004/27/EC. The new rank order is similar to our recommendation, and all Member States of the EU shall have to bring their national regulations into compliance with this Directive by no later than 30 October 2005.[18] ■

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Appendix 3: Analysis of 68 package inserts already available on the pharmaceutical market (4)

Original

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Analysis of German package inserts*

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package insert – comprehensibility – readability – patient information

Abstract. Objective: Package inserts have an important impact on patients compliance and thus on the effectiveness of drug use. Despite efforts of the European or national regulatory authorities and manufacturers to improve the readability and comprehensiveness of package inserts, they are still the subject of critical discussion. Material and methods: 68 German package inserts were chosen for a detailed analysis of their quality and suitability based on a set of 104 quality criteria developed prior to the survey. Results: In many cases package inserts available on the German drug market did not include important information or were difficult to read or understand. In 73.5% of cases, the daily maximum dose was missing and 63.2% gave no information on the measures to take for each of the interactions. 66.2% of package inserts provided no instructions about the correct storage and 58.8% gave no instructions on the appropriate storage temperature. In 13 cases, dosage instructions were provided only in milligrams of active substance instead of a number of tablets or volume of liquid. 98.5% of the 68 package inserts included non-quantifiable statements such as "high dosage" or "take 2 – 4 tablets, 1 – 3 times daily". 97.1% contained repetitious information, 83.8% included advertising elements and 8.8% contained contradictory information. Conclusion: Package inserts must be optimized and tested by selected groups of patients prior to approval of the drug. This will avoid misunderstandings and lack of information and ensure that use of the drug will give the best possible outcome and avoid safety risks.

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Introduction

Package inserts are important because they provide essential drug information. They should inform patients about the drugs, improve the success of treatment and, in particular they should increase drug safety [EFPIA 2003, The European Parliament and the Council of the European Union 2001]. Directive 2001/83/EC of the European Parliament and the Council stipulates that in every Member State of the European Union all medicinal products for human use shall include a package insert [The European Parliament and the Council of the European Union 2001]. Package inserts are therefore one of the most frequently used sources of drug information. In surveys 70 – 85% of patients indicated that they always or often read the package inserts to inform themselves about their medicines [Fuchs et al. 2003, Vander Stichele et al. 1991, Weitbrecht and Vosskaemper 2002].

Despite the efforts by the European and national regulatory authorities and the manufacturers to improve the readability and comprehensibility of package inserts the usefulness of them is still under discussion. Important points of criticism include comprehension (because they often use highly technical words), the small font size and the extensive amount of information included [Bernardini et al. 2000, Fuchs et al. 2005]. Some articles report that reading package inserts can make patients uncertain about their therapy or stop them using their medication [Fuchs et al. 2003, Van Haecht et al. 1991, Vander Stichele et al. 1991].

The following survey was carried out to examine a number of aspects that influence the comprehensiveness and readability of package inserts. In addition, the availability of important patient information was also examined.

Method

A set of 104 quality criteria for evaluating package inserts were developed prior to the survey [Fuchs 2004]. The criteria included recommendations for package inserts based

on the European and German drug laws [N.N. 1998, The European Parliament and the Council of the European Union 2001] and also included general instructions for easily understandable and clearly legible written information in the German language [Christmann and Groeben 1999, Hohgräwe 1988].

The rating pharmacist did not know the content and design of the 68 selected package inserts at the beginning of the survey. The analyzed versions were from:

- commonly used drugs (n = 68),
- products from different manufacturers (n = 36),
- drugs with different therapeutic indications (n = 43) and application forms (n = 19) and
- drugs available on the German market during the first 6 months of 2000 (n = 68).

All package inserts chosen were assigned to one of the following three groups:

- Group A: drugs with national registration in Germany and available only on prescription (n = 34, drugs of the 20 most prescribed therapeutic indication groups in Germany in 1997 [Schwabe and Pfaffrath 1999]),
- Group B: over-the-counter drugs with national registration in Germany (n = 23, frequently bought over-the-counter drugs in the first quarter in 1999 [IMS Health 1999]) and
- Group C: drugs with European registration, only available on prescription (n = 11, choice of available drugs at the time of the analysis [N.N. 1999]).

Results

Analysis of content

The date of last update in 89.7% of all package inserts was between 1997 and 1999. Four versions failed to include this information.

All package inserts contained information on therapeutic indication, contraindications, interactions, dosage instruction, possible adverse drug reactions and storage. However, an in-depth analysis using the 104 criteria revealed some differences:

Contraindications

5 package inserts failed to include specific instructions on measures necessary to deal with all the contraindications. Information on possible use during pregnancy was missing in four package inserts and in nine cases advice on use during lactation was missing.

Instructions on possible application to children and the elderly could only be found in 64.7% and 25.0% of all versions, respectively. Of these package inserts, 16 provided no information on the age of the children and 10 provided no information on the age group of the elderly. There were no significant differences between the three groups.

Interactions

Only 36.8% of all package inserts examined included recommendations on suitable measures for dealing with the listed interaction. Versions in Group A had significantly lower results in this quality criterion (13.3%) and versions in Group C the highest (100%).

Dosage instruction

All package inserts analyzed included information on the form of consumption and dosage of the medication. However, 13 of them provided dosage instructions only in milligrams of active substance instead of a unit dose such as 2 tablets or 1 capsule. Among the 68 package inserts, there were 29 cases with non-specific statements with regard to the dosage instructions (e.g. take 2 – 4 tablets, 1 – 3 times daily without an explanation as to the use of 2 or 4 tablets) (Table 1).

Only 26.5% of all versions included the maximum daily dose. Approximately three quarters of these (n = 18) gave this dosage instruction as a number of tablets or capsules or as volume (Table 1).

Advice on the period of use was available in 55 cases. Most (94.6%) included this information in the form of a number. 77.8% of package inserts for non-prescription drugs provided advice on when to consult a medical doctor.

39.7% of the 68 versions described the time of the day when the medication should be used. 48 of 56 inserts for oral-used prepa-

Table 1. Package inserts (n = 68) which meet the quality criteria of dosage instructions (selection of quality criteria; n.s. = not significant).

Quality criteria	All versions	Meet quality criteria Group A	Group B	Group C	Differences (p*) A/B	A/C	B/C
Dosage instructions are available	100% n = 68	100% n = 34	100% n = 23	100% n = 11	n.s.	n.s.	n.s.
All dosage instructions are given as number of tablets or capsules or as volume, drops or amount of the drug	80.6% n = 67	72.7% n = 33	91.3% n = 23	81.8% n = 11	n.s.	n.s.	n.s.
Non-quantifiable dosage as instructions such as 1 – 3 times, 2 – 4 tablets without an explanation are missing	57.4% n = 68	52.9% n = 34	43.5% n = 23	100% n = 11	n.s.	0.009	0.002
Information such as take the medicine "to", "before" or "independent" of a meal are available in the case of orally taken drugs	85.7% n = 56	85.7% n = 28	83.3% n = 18	90.0% n = 10	n.s.	n.s.	n.s.
The maximum daily dose is included	26.5% n = 68	23.5% n = 34	30.4% n = 23	27.3% n = 11	n.s.	n.s.	n.s.
The maximum daily dose is given as number of tablets, capsules or volume	72.2% n = 18	87.5% n = 8	71.4% n = 7	33.3% n = 3	n.s.	n.s.	n.s.
Hints on the period of use are available	80.9% n = 68	88.2% n = 34	78.3% n = 23	63.6% n = 11	n.s.	n.s.	n.s.
The type of solution to use is given for orally taken drugs with a solid application form	38.5% n = 39	29.4% n = 17	33.3% n = 12	60.0% n = 10	n.s.	n.s.	n.s.
The amount of solution to use is given by orally taken drugs with a solid application form	20.5% n = 39	29.4% n = 17	16.7% n = 12	10.0% n = 10	n.s.	n.s.	n.s.
Hints on the divisibility of orally taken drugs with solid application form are given	34.1% n = 41	61.1% n = 18	15.4% n = 13	10.0% n = 10	0.025	0.016	n.s.

*U-test (Mann and Whitney).

rations gave information such as: take the medicine "to", "before" or "independent" of a meal. Should the preparation be required to be taken before a meal, then a quantifiable time for consumption was given by only 20% (Table 1).

38.5% mentioned the kind of liquid to be used with solid medications (such as tablets or capsules) taken orally (n = 39) and only 20.5% included information on the amount of liquid. Recommendations that tablets and capsules should be taken in an upright position [Gallo et al. 1996] was missing in all cases (Table 1).

Whether it was possible to divide i.e. break oral preparations such as tablets was included in 34.1% of package inserts (Table 1).

Hints on application errors

If patients make administration errors, they will need information on suitable measures [The European Parliament and the Council of the European Union 2001]. In 10 cases however, this important information was missing.

Table 2. Means, minimums and maximums different aspects of the comprehensibility, readability and extent from package inserts (n = 68) (n.s. = not significant).

	All versions			Mean of the groups			Differences (p*)		
	mean	min	max	A	B	C	A/B	A/C	B/C
Foreign words of all words (%)	3.3	0.3	10.7	4.5	2.2	1.7	< 0.001	< 0.001	n.s.
Non-quantifiable statements in 100 sentences (n)	14	0	33	15.8	16.7	4.9	n.s.	< 0.001	< 0.001
Abbreviations in 100 sentences (n)	12	0	31	13.0	12.5	4.9	n.s.	< 0.001	= 0.001
Repetitions in package inserts (n)	3	0	18	4.4	2.5	2.7	= 0.001	0.021	n.s
Brackets in 100 sentences (n)	34	7	81	42.4	29.3	16.6	0.007	< 0.001	0.005
Words in package inserts (n)	1,496	365	3,375	1,911	998	1,253	< 0.001	0.002	n.s.
Sentences in package inserts (n)	95	24	194	118	64	89	< 0.001	0.012	0.007
Sentences with more than 20 words (%)	19.3	6.8	36.7	20.9	19.0	15.2	n.s.	0.012	n.s.
Words with more than 20 letters (%)	0.9	0	3.7	1.1	1.1	0.3	n.s.	< 0.001	< 0.001
Number of advertising elements in package inserts (n)	1	0	3	0.9	1.1	0.9	n.s.	n.s.	n.s.
Font size (pt)	8	6	11	7.8	8.3	8.5	n.s.	0.008	n.s.
Paper weight (g/m^2)	53.0	40.0	133.5	51.3	52.9	58.2	n.s.	n.s.	n.s.

*U-test (Mann and Whitney).

In addition, only 40.0% and 55.6% of package inserts for drugs available only on prescription, Group A and C respectively, included information on possible side effects after stopping the medication or changing the dose without advice of a doctor.

Possible adverse drug reactions

Only one of the 68 inserts gave quantitative information in numbers regarding the frequency of application and nine versions included the severity of every possible adverse drug reaction. However, this information was provided more frequently in package inserts of Group C drugs than in other groups.

In addition, only 63.2% of the package inserts provided information on the possible influence of the medication on reaction time after using the medicine. Here the package inserts of Group C also ranked significantly better than those for the other groups. However, only every second version with this information gave advice on the capability to drive a car or operate a machine.

51.2% of all analyzed package inserts included suitable measures for every adverse drug reaction. Only one of the 45 inserts for prescription-only medication gave an assessment on consumer benefit as compared with possible side effects.

Storage

Only 33.8% gave instructions on correct storage and 41.2% included no instructions on the appropriate storage temperature. Versions in Group C were significantly better in these two categories compared to the other groups.

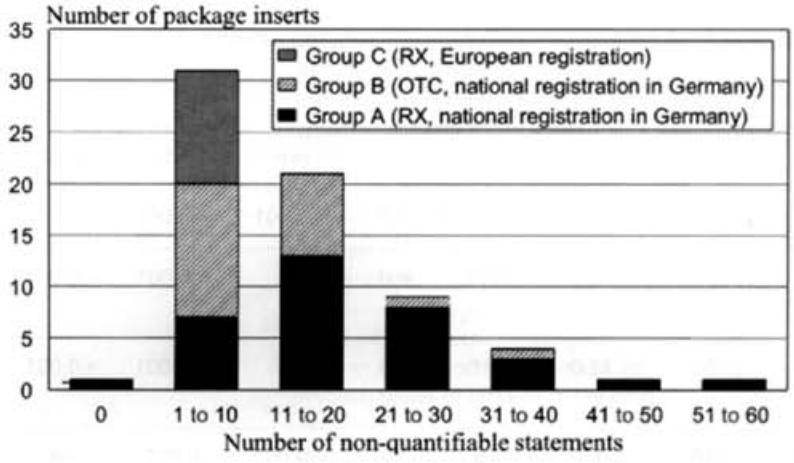

Figure 1. Number of non-quantifiable statements in package inserts (n = 68).

Every fifth package insert (20.0%) for preparations available only on prescription recommended: "Do not give this medication to other persons". Group C package inserts were again significantly better regarding this quality criterion.

38.2% of cases examined did not have more than one manufacturer's address. 85.3% of all versions included a telephone number, 69.1% a fax number and only 2.9% an internet address.

Analysis of comprehensibility and readability

Although the Directive 2001/83/EC and German drug law (AMG § 11) demand easily legibility and clearly comprehensible package inserts [N.N. 1998, The European Parliament and the Council of the European Union 2001], all 68 package inserts included foreign words which are usually more difficult to understand. These words were used significantly more often in versions of Group A (Table 2).

98.5% of package inserts contained non-quantifiable statements [Fuchs 2004]. For example "high dosage" or "use for a long time". The use of these terms was significantly lower in Group C (Table 2, Figure 1).

97.1% of all cases had repetitions or abbreviations, 83.8% included advertising elements and 8.8% contradictory information. One package insert had 18 repetitions of different contents, which markedly increased the length of this version.

Every fifth package insert (22.0%) contained more than 2,000 words. These were 3 – 4 written leaflets (size 210 × 297 mm) with a font size of 8 pt. Versions of Group A appeared to have more words than the others. Package inserts with European approval (Group C) used the shortest sentences and the least number of words (Table 2).

A font size larger than 10 pt occurred in only one package insert. The average font size was 8 pt (Table 2).

Discussion

It is concluded from these results that patients will probably not fully understand any of the 68 package inserts under study and therefore will not be able to follow the instructions to their best possible benefit. It is most likely that this conclusion also applies to other package inserts on the German market.

Providing dosage instructions only in milligram of active substance is a well-known problem in drug safety. The survey PAINT (package insert test) showed that up to 90% of patients do not understand this type of dosage instruction [Fuchs et al. 2004].

Other sources of potential mistakes in comprehensibility are due to non-quantifiable statements as found in non-specific dosage instructions (e.g. take 2 – 4 tablets, 1 – 3 times daily) and qualitative statements on the frequency of side effects (e.g. rare or common) [Fuchs 2004].

Berry and colleagues [2002] showed that qualitative descriptions of adverse drug reactions led to gross overestimation of risk. Students at Reading University (n = 200) found that the qualitative term "very rare" occurred with a mean frequency of 4% (EU assigned frequency: < 0.01%).

The European Commission [1998] recommended a method for testing the comprehensibility and readability of package inserts. However, it is not obligatory to test every package insert. Additionally, an obligatory standard method for testing all versions is not available.

We recommend therefore that every package insert be examined with regard to non-quantifiable statements, foreign words, ab-

breviations and measures taken to ensure that they contain all the important information using a standardized set of quality criteria.

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More information about the analyzed package inserts are available by the authors.

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