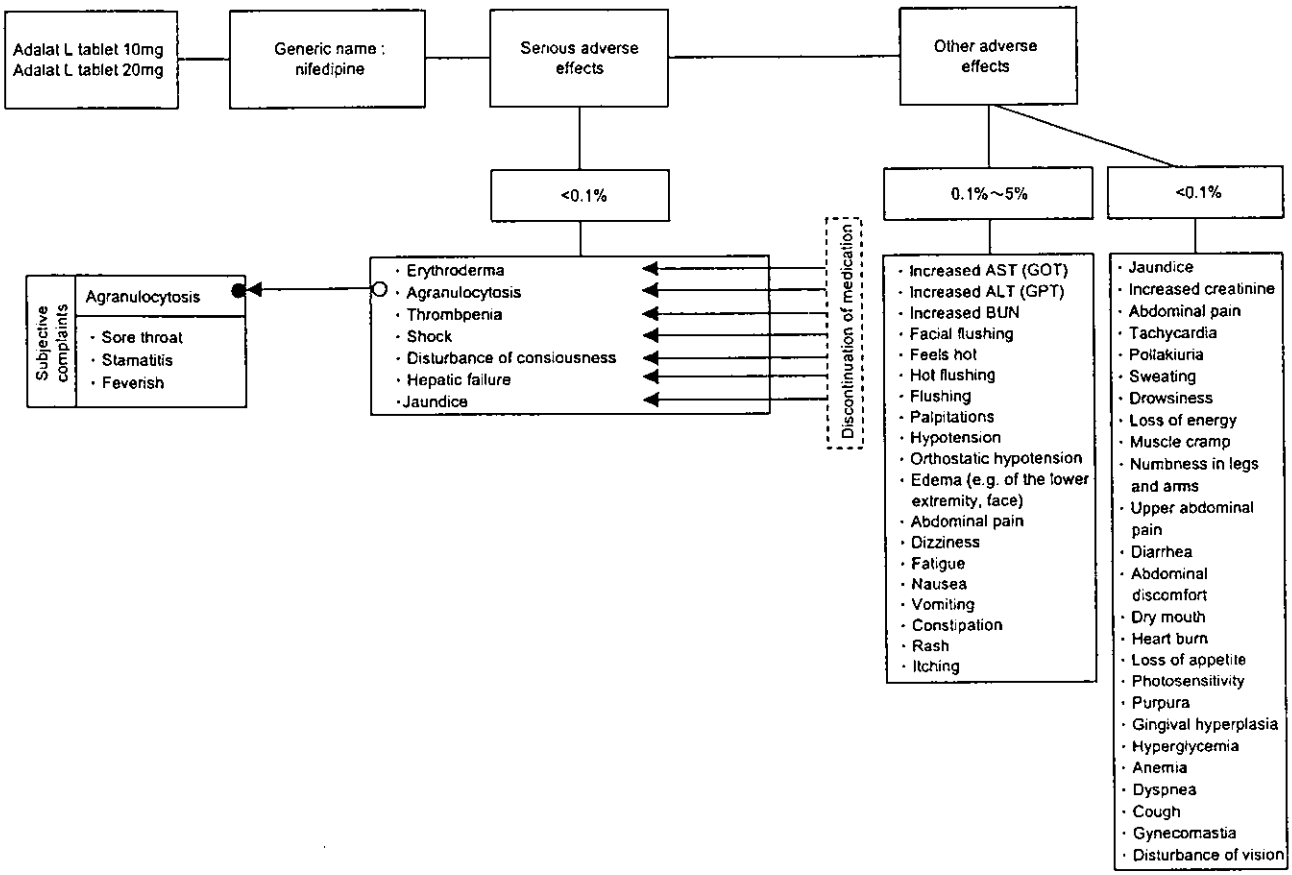


Figure 4. An example showing association between adverse effects listed in order of severity and subjective symptoms

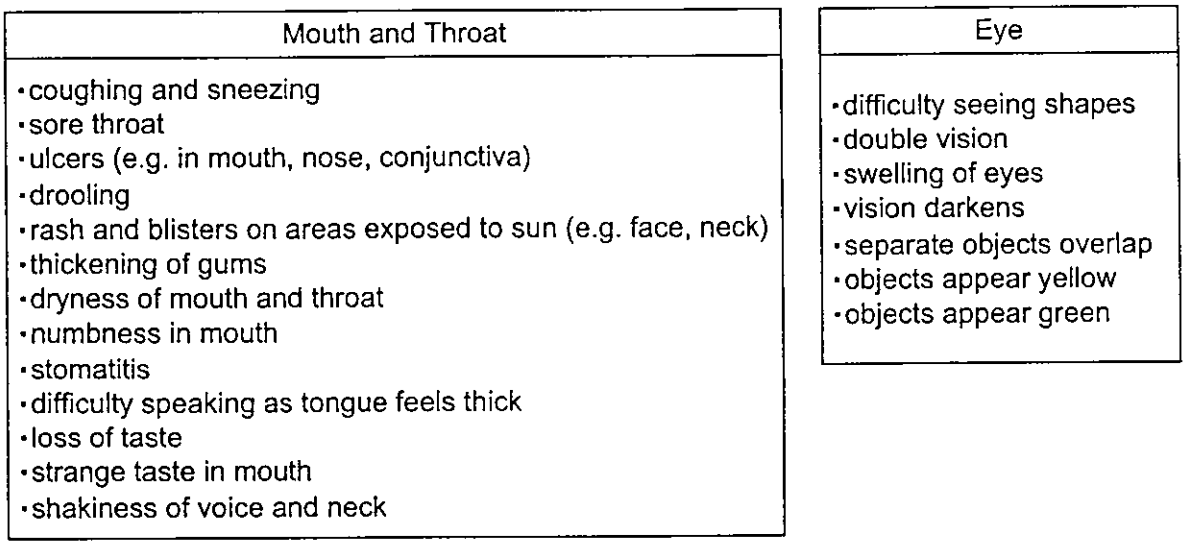


Figure 5. An example of subjective complaints classified by areas of the body

digoxin. Conversely, the adverse effects indicated by "feeling nauseous" were "fulminant hepatitis" and "nausea" for benzbromarone, "upper-abdominal pain" for nifedipine, "nausea" for digoxin and furosemide (**Figure 8**).

We also examined a 77 years old male with hepatic and renal failure using the same regimen, 52 adverse effects were listed. Of the top 12, "poor appetite" was associated only with furosemide. The implied adverse effects were "aplastic anemia", "Stevens-Johnson syndrome", "anemia", "orthostatic hypotension", "loss of appetite", and "hyponatremia". The

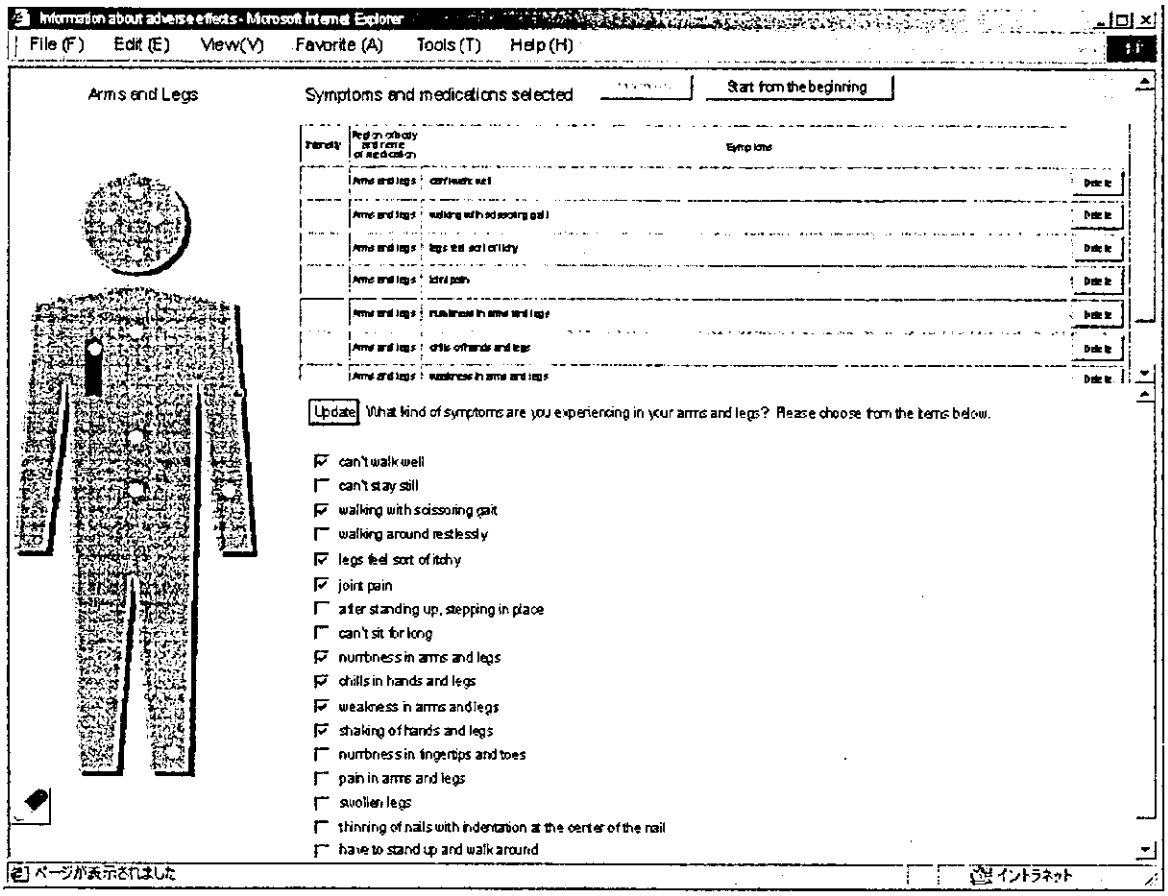


Figure 6. Ten areas of the body and subjective complaints (Example)

subjective complaint of "feeling nauseous" was related to "fulminant hepatitis" and "nausea" for benzbromarone, and "nausea" for furosemide (**Figure 9**).

The results indicate that users are able to identify potential adverse effects based on subjective complaints of patients who have been administered multiple medications using a scoring system that lists the adverse effects in order of severity. In addition, it is possible to differentiate between the degrees of severity of adverse effects by inputting the patient's medical condition.

Healthcare professionals are also able to view the search results, and thus determine whether symptoms are related to adverse effects or other factors.

We categorized scores of more than 200 as high, between 100 and 199 as medium, and between 30 and 99 as low in order to prepare the self-monitoring list, so as to determine how subjective symptoms in the above examples would be evaluated. In the case of the 62 years old male, "poor appetite" was categorized as moderately serious, and "feeling nauseous" was categorized as not so serious. In the case of the 77 years old male, both "feeling nauseous" and "poor appetite" were categorized as very serious. The self-monitoring list recommended to the 62 years old male that he observe his symptoms closely for a while, while it recommended to the 77 years old male to visit a physician immediately. Therefore, the results demonstrate that the self-monitoring list is useful in suggesting to patients what action should be taken.

Assuming that the system will be used via the Internet, we need to take measures to protect patient information. Users should avoid entering data that might assist in identifying the individual, such as name, and should use measures to automatically close the Web browser. In the network, use of a Secure Socket Layer (SSL) that provides encrypted communication is recommended. The Web server should utilize a firewall to prevent invasion and to obtain certification from the Certification Authority in order to identify sources/incidences of unauthorized access.

Discussion

The present study aimed to prepare an environment in which patients can identify adverse effects in the early stages through self-monitoring. We attempted to identify the best method for healthcare professionals to provide information to patients utilizing subjective complaints in patient's understandable language and to establish a system such that even when patients are administered multiple medications, users can search for and identify potential adverse effects based on subjective complaints. We also created an information printout for patients using subjective complaints in patient's understandable language. The results indicate the feasibility of this method in clinical practice and its potential usefulness in society.

The system allows healthcare professionals to obtain

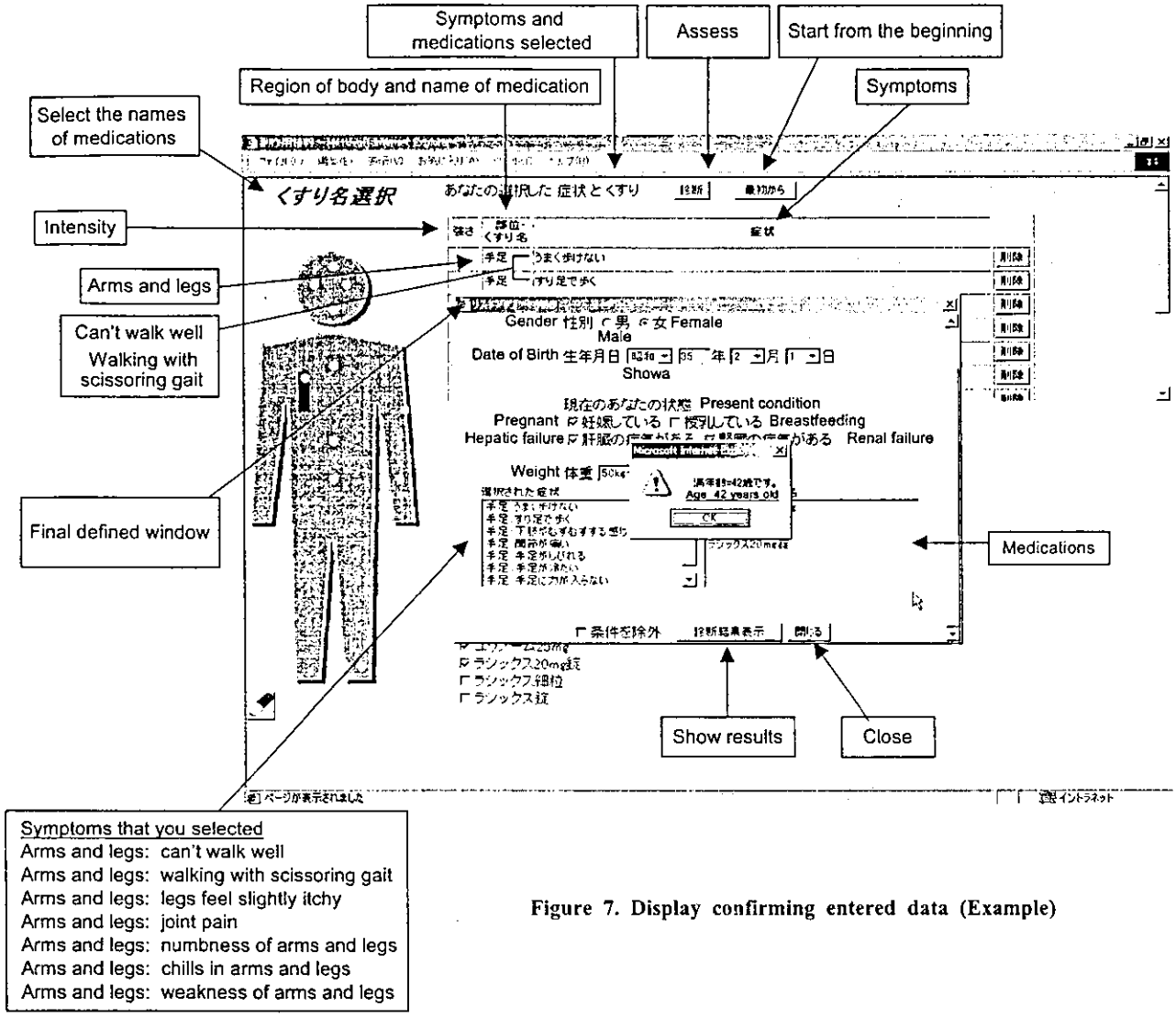


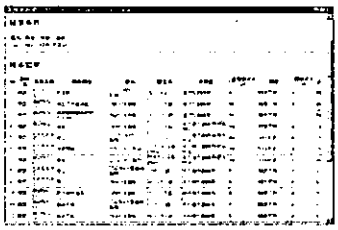
Figure 7. Display confirming entered data (Example)

information about adverse effects that patients should watch for, including the degree of severity and the incidence, and to provide information using patient's understandable language. In addition, patients can also access the system. Patients are therefore provided with an environment in which they can seek information anytime and anywhere. The instructions are provided to patients, who learn that their subjective complaints are associated with drug adverse effects. This can lead to early treatment and enhance patient safety. Future studies should examine the degree to which we can depend on self-care.

Drug-drug interaction is important factor in the production of adverse effects. At present, as there are many information of the drug-drug interaction, it becomes to be possible to avoid the adverse effects concerning the drug-drug interaction. Accordingly, in the present study, cumulative or additive drug effects are especially focused.

Finally, the format of the information printout for patient use becomes to be similar to the United States Pharmacopeia-Drug Information (USP-DI)[5]. However, support system for the detection of adverse effects in the early stage to patients prescribing multiple medications is not found anywhere including Japan in the present time.

This system enables healthcare professionals to obtain lists that link adverse effects in order of severity with various medications. Therefore, if subjective complaints are associated with adverse effects, healthcare professionals will be able to identify the responsible medication. If the probability of association with the adverse effects is low, they will be able to focus on other factors, such as the effects of illnesses. The results indicate that this system is helpful for clarifying causal factors, and in supporting early action in clinical practice. In the past, identifying the adverse effects of medications has relied on the experience of healthcare professionals. Using this new system, however, objective evaluation can be performed. Inexperienced healthcare professionals will therefore also be able to obtain a certain level of ability to evaluate the safety of medications. In the present situation, healthcare professionals need to examine the adverse effect information for each medication to identify the potential adverse



Search condition

Name	Weight	Age	Condition
aaa	50 kg~	62	none

Search results

No.	Areas of the body	Subjective complaints	Adverse effects	Generic name	Trade name	Degree of severity of adverse effects	Score of severity	Incidence	Score of Incidence	Displayed by descending order of the total score
1	abdomen	feeling nauseous	fulminant hepatitis	benzbromarone	Urinorm	Serious adverse effects	15	unknown	4	19
2	abdomen	poor appetite	aplastic anemia	furosemide	Lasix	Serious adverse effects	15	unknown	4	19
3	abdomen	poor appetite	Stevens-John son syndrome	furosemide	Lasix	Serious adverse effects	15	unknown	4	19
4	abdomen	poor appetite	anemia	furosemide	Lasix	Other adverse effects (discontinue medication)	10	unknown	4	14
5	abdomen	feeling nauseous	nausea	benzbromarone	Urinorm	Other adverse effects (discontinue medication)	10	<0.1%	1	11
6	abdomen	feeling nauseous	upper abdominal pain	nifedipine	Adalat L 20 mg	Other adverse effects (discontinue medication)	10	<0.1%	1	11
7	abdomen	poor appetite	anemia	nifedipine	Adalat L 20 mg	Other adverse effects (discontinue medication)	10	<0.1%	1	11
8	abdomen	feeling nauseous	nausea	digoxin	Digosin	Other adverse effects	5	unknown	4	9
9	abdomen	feeling nauseous	nausea	furosemide	Lasix	Other adverse effects	5	unknown	4	9
10	abdomen	poor appetite	orthostatic hypotension	furosemide	Lasix	Other adverse effects	5	unknown	4	9
11	abdomen	poor appetite	loss of appetite	digoxin	Digosin	Other adverse effects	5	unknown	4	9
12	abdomen	poor appetite	loss of appetite	furosemide	Lasix	Other adverse effects	5	unknown	4	9

Figure 8. Table not including patient condition (Initial Screen)

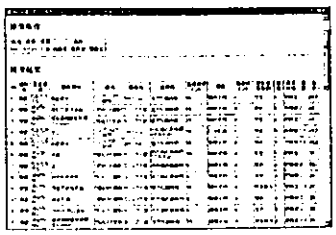
effects. This may take a substantial amount of time, potentially resulting in exacerbation of patient condition. This situation would be improved immediately and will also ensure maximal safety of patients. Pharmacists spend a large amount of their time collecting, processing, and supplying drug information, which can change frequently and sometimes drastically. We believe that pharmacists need to improve the efficiency of their work in future by utilizing internet technology, and they should also handle information about adverse effects and subjective complaints as universal information, in order to practice more patient-oriented services as a member of a clinical team. The outcome of the present study is therefore useful for improving safety measures.

The present study suggests several issues that need to be addressed in the future. As the validity of the model must be evaluated by adding various conditions in this study, we examined cases involving patients who were prescribed only five active ingredients. In the future, combinations of greater numbers of medications must be investigated. In addition, regarding usage of the scoring system to predict the degree of severity and incidence of adverse effects, issues such as validity of scores and which value of total scores should be used as criteria to recommend patient visits to the physician need to be resolved objectively. We believe that statistical methods would be appropriate for the solution. In addition, patients express various subjective complaints. The EISEUD used in this study as the basic data also shows that one adverse effect is associated with many subjective complaints in patient's understandable language. This may confuse both healthcare professionals and patients when healthcare professionals provide information to the patients. To prevent this, some degree of standardization of subjective complaints is necessary and will be discussed at another time.

The person who provides the final advice resulting from the subjective complaints is the healthcare professional, such as a physician or pharmacist. We confirmed that the present system is able to support the provision of appropriate information at a certain level for the collection and supply of safety information for patients and healthcare professionals. In future, more medications need to be examined.

Acknowledgment

This study was conducted as part of the "Research for Collection and Provision of Appropriate Information to Enable



Search condition

Name	Weight	Age	Condition
aaa	50 kg?	77	Elderly, hepatic failure, renal failure

Search results

A. warning, contraindication, relative contraindication, or careful administration
B. score
C. multipliers

No.	Areas of the body	Subjective complaints	Adverse effects	Generic name	Trade name	Degree of severity of adverse effects	Score of severity	Incidence	Score of incidence	A	B	Conditions of the patient	C	Displayed by descending order of the total score
1	abdomen	feeling nauseous	fulminant hepatitis	benzbromarone	Urinorm	Serious adverse effects	15	unknown	4	warning	5	Hepatic failure	2.7	64.8
2	abdomen	poor appetite	aplastic anemia	furosemide	Lasix	Serious adverse effects	15	unknown	4	contraindication	4	Hepatic failure	2	48
3	abdomen	poor appetite	Stevens-Johnson syndrome	furosemide	Lasix	Serious adverse effects	15	unknown	4	contraindication	4	Hepatic failure	2	48
4	abdomen	feeling nauseous	nausea	benzbromarone	Urinorm	Other adverse effects (discontinue medication)	10	<0.1%	1	warning	5	Hepatic failure	2.7	43.2
5	abdomen	feeling nauseous	fulminant hepatitis	benzbromarone	Urinorm	Serious adverse effects	15	unknown	4	contraindication	4	Renal failure	1.6	38.8
6	abdomen	poor appetite	anemia	furosemide	Lasix	Other adverse effects (discontinue medication) contraindication	10	unknown	4	contraindication	4	Hepatic failure	2	36
7	abdomen	feeling nauseous	nausea	furosemide	Lasix	Other adverse effects	5	unknown	4	contraindication	4	Hepatic failure	2	26
8	abdomen	poor appetite	orthostatic hypotension	furosemide	Lasix	Other adverse effects	5	unknown	4	contraindication	4	Hepatic failure	2	26
9	abdomen	poor appetite	aplastic anemia	furosemide	Lasix	Serious adverse effects	15	unknown	4	careful administration	1	Renal failure	1.3	26
10	abdomen	poor appetite	loss of appetite	furosemide	Lasix	Other adverse effects	5	unknown	4	contraindication	4	Hepatic failure	2	26
11	abdomen	poor appetite	hyponatremia	furosemide	Lasix	Other adverse effects	5	unknown	4	contraindication	4	Hepatic failure	2	26
12	abdomen	poor appetite	Stevens-Johnson syndrome	furosemide	Lasix	Serious adverse effects	15	unknown	4	careful administration	1	Renal failure	1.3	26

Figure 9. Table including patient condition (Initial Screen)

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References

1) Ministry of Health, Labour and Welfare. The outcome of the research: Status of the use of medications, classified by type of national medical care 1999
2) Japan Pharmacists Education Center (Ed.). Safety Division of the Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare (supervisor). Standard Essential Information for Safe and Effective Use of Drugs. Jiho, Inc. 2000
3) Ministry of Health, Labour and Welfare. Drug Information Supply System.
4) Uchiyama M. Research on the method to standardize the terminology of adverse effects for patient use. *Pharmaceutical and Medical Safety Research*, Ministry of Health, Labour and Welfare. 2000
5) 21st USP-DI Advice for the patient: Drug information in lay language. NJ: Micromedex, Inc. 2001