—Regular Articles—

Objective Evaluation of Generic Drug Information

Hisashi IIJIMA,*[,a,b] Miwako KAMEI,[a] Toshimasa KOSHIMIZU,[c] and Makoto SHIRAGAMI[a]

Social and Administrative Pharmacy Science, College of Pharmacy, Nihon University,[a] Drug Information Center, Chiba Pharmaceutical Association,[b] and Department of Pharmacy, Juntendo University Urayasu Hospital[c]

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Pharmacists active in health care venues need to be able to evaluate generic drugs in terms of effectiveness, safety, and economy to ensure that they are used appropriately. As part of the ongoing study of these factors, we carried out an objective evaluation of information provided for generics. A minimum of 20 commercially available products was considered for each pharmaceutical ingredient. The information subjected to evaluation consisted of the text of drug package inserts and information noted on interview forms. Using our own criteria for evaluating drug information, we attempted to quantify the amounts of information provided. Then, based on the numerical values obtained, we calculated information quantities with reference to drug prices to study the relationship between prices and available information for original drugs and their later-developed, generic equivalents. A total of 14 different pharmaceutical ingredients (327 product items) were considered, with the information quantity for generics amounting to 27.9±17.8—46.3±21.4% (Mean±S.D.) that for the original drugs. Examined on the basis of individual pharmaceutical companies, the corresponding ratio came to 15.1±7.8—62.4±6.4% (Mean±S.D.). For generics, the relationship between drug price (expressed against a value of 1.0 for original drugs) and information quantity (Qua_i) came to 0.79±0.46—1.90±0.79% (Mean±S.D.). These results clearly point to the importance of evaluating information quantity for generic drugs on a maker-by-maker basis.

Key words——generic drug; drug information; pharmaceutical industry; drug evaluation; necessity factor; drug price

INTRODUCTION

Japan has a universal health care system providing for compulsory enrollment of all citizens in some form of public health insurance plan. The patient's copayment is a fixed percentage of the overall cost. Under this system, the medical payments (including drug coverage) made by health insurance plans are set by the Ministry of Health, Labor and Welfare and ordinarily are subject to revision once every two years. In the revision that took place in 2002, additional amounts in the reimbursements to physicians issuing prescriptions for generic drugs were newly established, together with increases in reimbursements to pharmacies dispensing generics. Amidst the mounting pressure of medical expenses, use of generics will likely be promoted in the years to come. It is a hotly debated subject, however, and when incorporating generics into its drug price tariff, the Ministry of Health, Labor and Welfare instructed producers of generic drugs to make efforts to ensure a stable supply of generics and improve existing systems for collecting and supplying information.[1)]

e-mail: h-iijima@c-yaku.or.jp

Practicing pharmacists, on the other hand, need to be able to evaluate generic drugs in terms of effectiveness, safety, and economy to ensure that they are being used in an appropriate manner. We previously evaluated information quantities for 15 pharmaceutical ingredients (255 product items) in order to study the present state of generic drug information supply via paper media.[2,3)] However, upon determining scores for each piece of information, we found that they did not necessarily reflect the necessity of that information in medical care situations. We then conducted a new questionnaire survey of 1,000 medical institutions throughout Japan, revising our evaluation criteria to reflect necessity in medical care situations, for the drug information provided.[4)] In this report, we present the results of an objective evaluation of the quantities of generic drug information provided by paper media, based on these new evaluation criteria.

METHODS

Target Pharmaceuticals Our study targeted a minimum of 20 product items commercially available as of June 5, 2003, for each pharmaceutical under consideration. When branded versions of the drug are

sold by more than one company, we selected the version of the original drug receiving the greatest number of information points as the product used for comparison purposes in this study.

Quantification of Information The information that was the object of our evaluation was obtained from drug package inserts and interview forms (IF). In the case of the former, we omitted items that clearly did not differ from one product to another, such as drug approval information. With respect to IFs, we selected those pieces of information that our daily experience with drug information (DI) work had shown to be especially useful in medical care situations. These items were then incorporated into questionnaire forms sent out to 1,000 medical institutions having DI offices, located throughout Japan. Based on the results obtained from the 524 medical institutions responding to the questionnaire, we established a coefficient designated the ''necessity factor'' for each item of information[4] (Table 1).

Table 1. Drug Information Evaluation Criteria Score Chart

				Necessity factor
1. General outline	(1)	Development process		1.8
	(2)	Characteristics and usefulness of product		3.6
	(3)	Sales situation abroad		1.7
2. Active ingredient	(1)	Description		3.1
	(2)	Hygroscopicity		3.7
	(3)	Stability		3.4
3. Properties of the product	(1)	Description		3.2
	(2)	Additives		2.1
	(3)	Stability		3.3
	(4)	Drug interactions		4.1
	(5)	Dissolution test		1.4
4. Clinical data	(1)	Signature reason		4.4
	(2)	Clinical efficacy		3.8
	(3)	Clinical pharmacology review		2.4
	(4)	Exploratory trial		1.3
	(5)	Confirmatory trial		1.3
	(6)	Therapeutic use		2.6
5. Pharmacology	(1)	Mechanism of action		4.1
	(2)	Efficacy tests		2.4
6. Pharmacokinetics	(1)	Blood concentration	① Parameter (T_{max}, C_{max}, $T_{1/2}$, AUC, CL)	2.5
			② Effective concentration	3.3
			③ Toxic concentration	3.0
	(2)	Distribution	① Blood–brain barrier penetration	2.6
			② Placental barrier penetration	2.8
			③ Distribution to milk	2.9
			④ Distribution to cerebrospinal fluid	2.2
	(3)	Metabolism	① Metabolic pathway	3.5
			② Metabolic enzymes	2.3
			③ Percentage first-pass effected	2.2
			④ Percentage metabolized	2.2
			⑤ Parameter of active metabolite	1.9
	(4)	Excretion		3.5
7. Safety				4.2
8. Side effects				4.1
9. Non-clinical tests			(1) Pharmacological effect	1.6
			(2) Toxicity study (ID_{50}, ED_{50}, IC_{50})	1.5
		Total		100.0

On the basis of Table 1, we assigned scores to the various items of drug information for target pharmaceuticals. Totaling the ''necessity factor'' values for items of information provided by drug package insert or IF for each pharmaceutical studied, we determined the number of points for each target pharmaceutical.

Analysis Obtaining the percentage (DIr_i) of the generic drug information quantity (DI_i) based on the information quantity for the original drugs (DI_0) from Eq. (1), we compared quantities of information by ingredient, information item, and pharmaceutical company.

$$DIr_i(\%) = (DI_i/DI_0) \times 100 \quad (1)$$

Based on the various drug prices, we also determined the drug information quantity provided per unit of price (one Japanese yen), (DI/P). With the value for the original drugs (DI_0/P_0) as our reference value, we obtained Qua_i, the ratio DI_i/P_i for generic drugs, from Eq. (2).

$$Qua_i = (DI_i/P_i)/(DI_0/P_0) \quad (2)$$

Next, based on the calculated value for Qua_i, we used Eq. (3) to determine the hypothetical drug price at which the quantity of generic drug information provided per price unit was the same as that for the original drugs, i.e., the price at which $Qua_i = 1$.

$$\text{Drug Price} = \text{Current Drug Price} \times Qua_i \quad (3)$$

Drug prices current as of July 4, 2003 were used for these purposes.

RESULTS

Target Pharmaceuticals We identified 14 pharmaceuticals (327 product items) for which 20 or more product items were commercially available. For our therapeutic classifications, we employed 10 different pharmacological effect groups, with 4 of the drugs representing the category of cardiovascular agents and 2 others used in treating disorders of the digestive system (Table 2).

Evaluation of Information Provided by Paper Media In the comparison of drug information quantities by ingredient, we obtained 14.6±10.7—31.0±9.4 points (Mean±S.D.) for generic drugs as compared to 51.3—80.5 points for the original drug products. DIr_i, the generic drug information quantity ratio obtained from Eq. (1) based on the values for the original drugs, came to 27.9±17.8—46.3±21.4% (Mean±S.D.) (Fig. 1).

Our company-by-company comparison of average points for the 23 pharmaceutical makers selling 6 or more of the target pharmaceuticals used in this study yielded a result of 9.9±4.8—42.6±7.5 points (Mean±S.D.), while the ratio DIr_i based on the company developing the original, branded drug product came to 15.1±7.8—62.4±6.4% (Mean±S.D.) (Fig. 2).

Table 2. Drugs Studied

Ingredient	Classification	Item
Alfacalcidol	Vitamin preparations	23
Allopurinol	Antipodagric	24
Ambroxol hydrochloride	Agents affecting respiratory organs	30
Atenolol	Cardiovascular agents	23
Camostat mesilate	Agents affecting metabolism	20
Cilostazol	Hemotropic agents	20
Cimetidine	Agents affecting digestive organs	28
Enalapril maleate	Cardiovascular agents	22
Loxoprofen sodium	Antipyretic analgesics	27
Lysozyme chloride	Enzyme preparations	23
Oxatomide	Antiallergic agents	24
Probucol	Cardiovascular agents	20
Trimebutine maleate	Agents affecting digestive organs	20
Ubidecarenone	Cardiovascular agents	23

We also compared the average points of the original drugs for each of the item of information under evaluation to those of the generic drugs (Fig. 3). A large difference in information quantity between original drugs and generic drugs was observed in those items of information such as ''Therapeutic use,'' ''Safety'' or ''Side effects.''

Using the example of cilostazol, the target ingredient with the greatest variation in generic drug prices, we investigated the change of the drug information quantity provided by the original drug arising from each major revision of the IF, and found increases in point scores for ''Pharmacokinetics,'' ''Safety,'' and ''Side effects'' in the 8-year period from 1988 to 1996, as well as increases in points for ''Therapeutic use'' and ''Pharmacokinetics'' in the 7-year period from 1996 to 2003 (Fig. 4). Point scores did not decrease for any of the items of information.

Drug Information Based on Drug Price The generic drug information quantity per unit of price, Qua_i, obtained from Eq. (2) using the value for the original drug as the baseline, came to 0.79±0.46—1.90±0.79 (Mean±S.D.) (Fig. 1).

Our hypothetical generic drug price weighing the factor of drug information quantity, calculated with

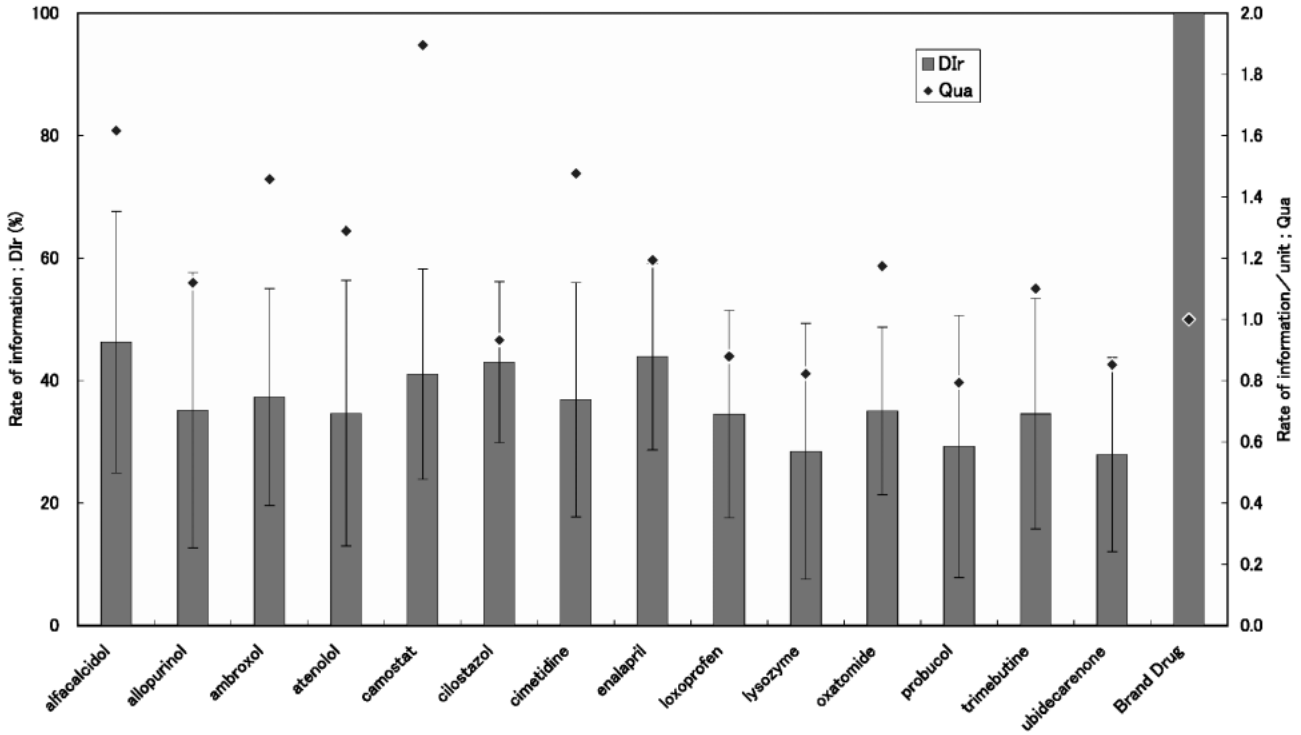

Fig. 1. The Ratio of the Generic Drug Information Quantity (DIr) and Generic Drug Information Quantity per Unit of Price (Qua) against the Original Drug

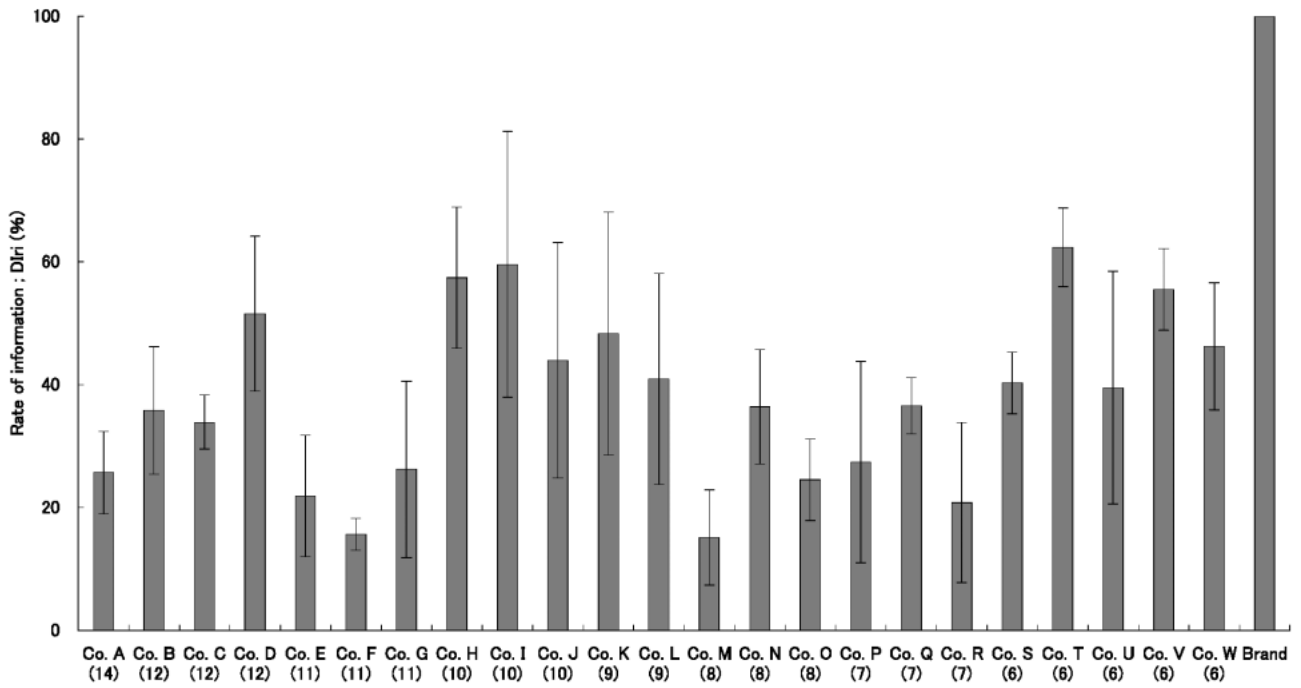

Fig. 2. Company-by-company Comparison of Drug Information Quantity

Eq. (3), came to 71.04—175.53 yen for cilostazol, the generic having the greatest number of price categories. This hypothetical price was higher than the present drug price for 7 of the cilostazol products on the market today; it was lower than the current price for 12 other cilostazol products (Fig. 5).

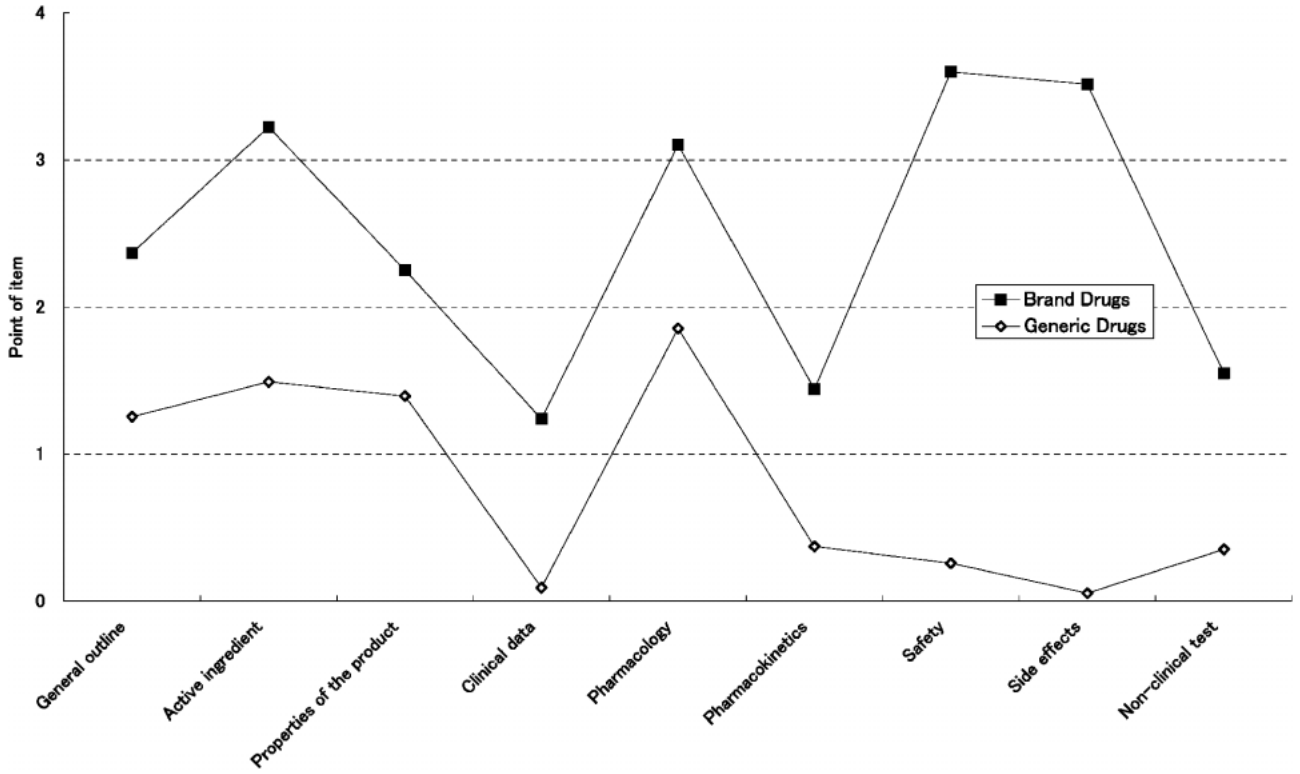

Fig. 3. Original Drug/Generic Drug Point Average for each of the Items of Information

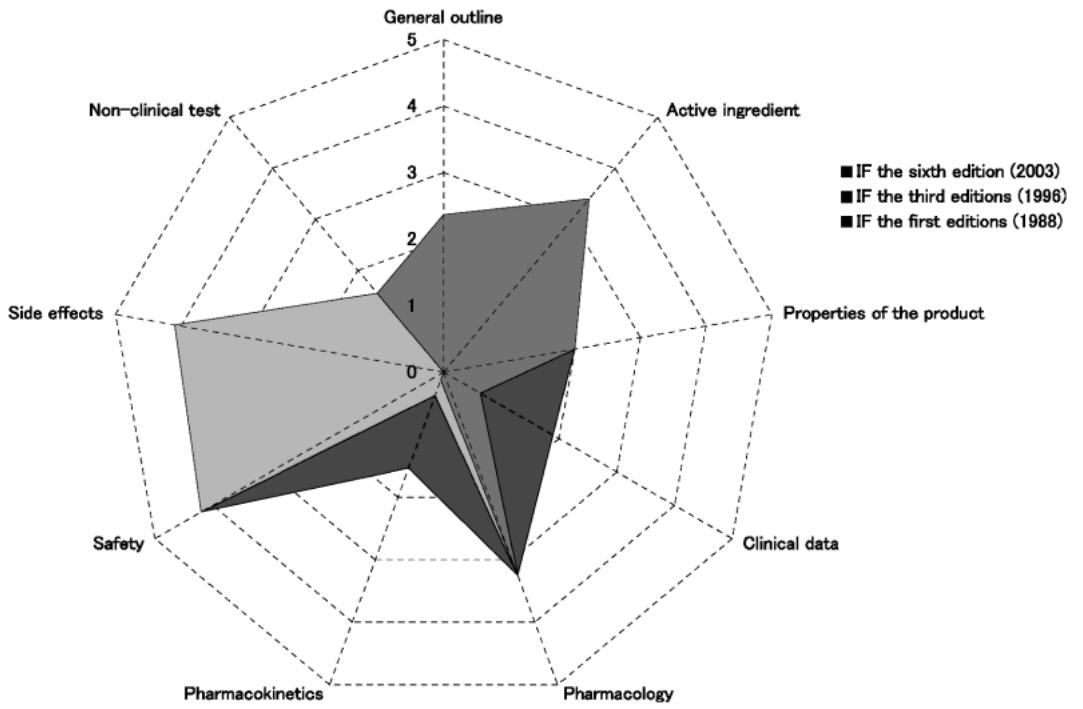

Fig. 4. Increase of the Drug Information Quantity Provided by the Original Drug (Cilostazol)

DISCUSSION

Examining 14 pharmaceuticals having 20 or more commercially available versions (total of 327 product items), we evaluated quantities of information provided for major generic drugs in Japan. From the

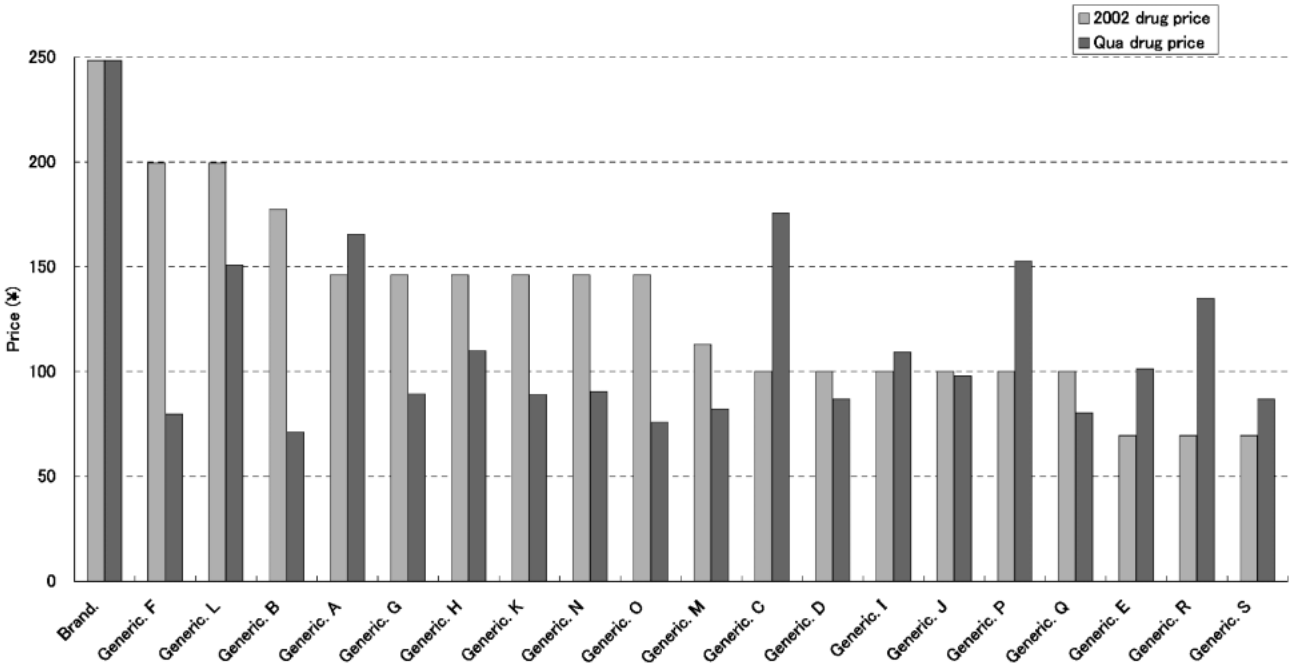

Fig. 5. Price on a Basis of Qua (Cilostazol)

standpoint of pharmacological effect, the greatest number of ingredients (4) represented drugs acting upon the cardiovascular system.

Evaluation of Information Provided by Paper Media Against a value of 100% for the quantity of information provided for the original drugs, the information quantity by ingredient came to 27.9±17.8—46.3±21.4% (Mean±S.D.) for generic drugs, indicating that the quantity of information provided for generics is less than half that for the original drugs (Fig. 1). However, since the data spread between products was large in this comparison by ingredient, we tried comparing information quantities according to pharmaceutical maker and obtained the result of 15.1±7.8—62.4±6.4% (Mean±S.D.), indicating that amounts of information provided for generic drugs differed from company to company (Fig. 2). It has been widely acknowledged for some time that the available information on generic drugs is inadequate. However, our results suggest that information on generics needs to be evaluated not from the standpoint of generic drugs in general, but in terms of individual drug makers.

The amount of information available on the original cilostazol has increased for information categories ''Pharmacokinetics,'' ''Safety,'' ''Side effects,'' and ''Therapeutic use'' (all items closely related to clinical applications) with each successive revision of the IF. This is thought to reflect the incorporation of results of post-marketing surveillance studies in drug information.

When we calculated the original drug/generic drug point average for each item of information, a large difference in information quantity was observed in those items of information such as ''Therapeutic use,'' ''Safety'' or ''Side effects.'' This result suggests that information on generics that does not fall within one of these three categories is based on the information available for the original drugs. These three categories are closely related to actual clinical use of the drugs. Compared with categories like ''Active ingredient'' and ''Development process,'' which are seldom revised, information in these three categories is subject to frequent change and needs to be augmented, even for generic drugs. It is, of course, true that under these evaluation criteria, the category of ''Side effects'' is based on observations made at the time of drug investigations, reexaminations, or efficacy reviews, while ''Therapeutic use'' is based upon data obtained from clinical trials of the drug, and there are some cases in which it is difficult for the makers of generic products to obtain the pertinent information. However, it should be possible to further expand information under these categories even for generics through collection, evaluation, and analysis of post-marketing results. Moreover, even makers of generic

products can obtain information on ''Safety'' from the existing literature, and this could form the basis for information printed on drug package inserts. Thus, improvement of information quantities for generics through searches of existing literature can be expected.

Drug Information Based on Drug Price The value of Qua_i obtained from Eq. (2) was equal to 1.0 if the quantity of information per unit of price was the same for generics as for the original drugs. We calculated Qua_i for our 14 generic pharmaceuticals, obtaining a value of 0.79 ± 0.46—1.90 ± 0.79 (Mean $\pm$S.D.) (Fig. 1). Hypothetically, if drug price were tied to information quantity, the prices of products with Qua_i values exceeding 1.0 (i.e., products for which makers provide ample information) would be raised, while the prices for items with Qua_i values of less than 1.0 (products on which the amount of information provided is inadequate) would be lowered.

In Japan today, the Ministry of Health, Labor and Welfare makes a general practice of setting the price for new pharmaceuticals at the same level as that for the equivalent existing drug when incorporating new items into its drug price tariff. Additional price increments are tacked on for any new products that are superior to the existing drugs in terms of effectiveness or safety. As a general rule, the price for generics is set at 80% of that for the original drugs. Once the product has been listed on the drug pricetariff, its price is revised once every 2 years on the basis of market transaction prices. At present, the quantity of information available on new drug products is not taken into consideration in these processes at all. For instance, in the case of the drug cilostazol, the hypothetical price calculated with Eq. (3) was higher than the present drug price for 7 of the products on the market today and lower than the current price for 12 other cilostazol products (Fig. 5).

More than a year has passed since increases were made in reimbursements to physicians prescribing generic drugs and pharmacies dispensing them, but much concern remains about the quality and supply of generics, as well as the quantity of information on these products provided by the makers. However, these problems do not pertain to generic drugs in general; availability of information varies from maker to maker. The present evaluation can serve as an aid to practicing pharmacists in their selection of products offering ample drug information, from among the numerous generics available, and it is hoped that these results will form the basis for improvements in information supply on the part of pharmaceutical companies. Of course, information on generic drugs is not provided solely by drug package inserts and IFs. The information provided by MRs (medical representatives) is also important. A comprehensive evaluation of information provision activities from all of these sources will need to be conducted in the future.

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