Present State of New Chiral Drug Development and Review in Japan

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The current situation of chiral drug development in Japan was investigated. The trend in the Japanese pharmaceutical development is increasingly moving towards the development of single isomers rather than racemates. The development of single-enantiomer drugs was made possible by the current technologies of asymmetric synthesis and chiral separation, and encouraged by the guidelines on the development of chiral drugs worldwide. Japan has not issued specific guidelines on the development of chiral drugs, however, the chiral drug development approached in Japan were essentially consistent with the approaches recommended by the U.S.A. and EU guidelines.

Key words —— chiral drug, single-enantiomer drug, racemic drug, pharmaceutical development, guideline

INTRODUCTION

Pharmaceuticals with an asymmetric carbon (chiral center) are often referred to as chiral drugs. Chiral drugs were mainly presented as the racemate, which is a mixture of equal amounts of left- and right-handed enantiomers. Two enantiomers in a racemate show completely identical physical and chemical properties when they are in an achiral environment. However, in a chiral environment such as *in vivo*, they demonstrate different chemical, biochemical, and pharmacologic behaviors. In principle, therefore, enantiomers in a racemic drug should be treated as two different compounds.

Although single-enantiomer drugs have been thought to be preferable to racemic drugs, most chiral drugs were developed as racemates due to the lack of technologies that produce single-enantiomers until recently. Current technologies of asymmetric synthesis and chiral separation made it possible for pharmaceutical companies to develop single-enantiomer drugs. Lately, many single-enantiomer drugs have been approved and marketed broadly. The Japanese government approved single-enantiomer drugs four times as much as racemic drugs in early 2000 s, although there was not significant difference in the number of approved drugs between racemic and single-enantiomer drugs in early 1990s (Fig. 1). The trends in world development and approval of chiral drugs were similar; the worldwide market share of single-enantiomer drugs increased from 27% in 1996 to 39% in 2002.[1–3)]

Pharmaceutical companies cannot market new drugs in Japan and in other regions until approved by the regulatory authorities, and they have to submit technical documents for new drug applications. The regulatory authorities evaluate the content of the technical documents to assure quality, efficacy and safety. In order to assure drug quality[4)] in Japan, specifications and critical manufacturing processes are needed to be written in legally binding approval documentation. In contrast, almost all of subjects described in technical documents are considered as legally binding matters in other countries. As a result, approval matters on quality-related issues are often different between Japan and other countries.

We considered it important to research what kinds of data are to be collected during the development of chiral drugs and how the regulatory authorities evaluate these data. Additionally it is valuable to realize what kinds of issues are dealt with as legally binding matters. The findings can provide common understanding between pharmaceuti-

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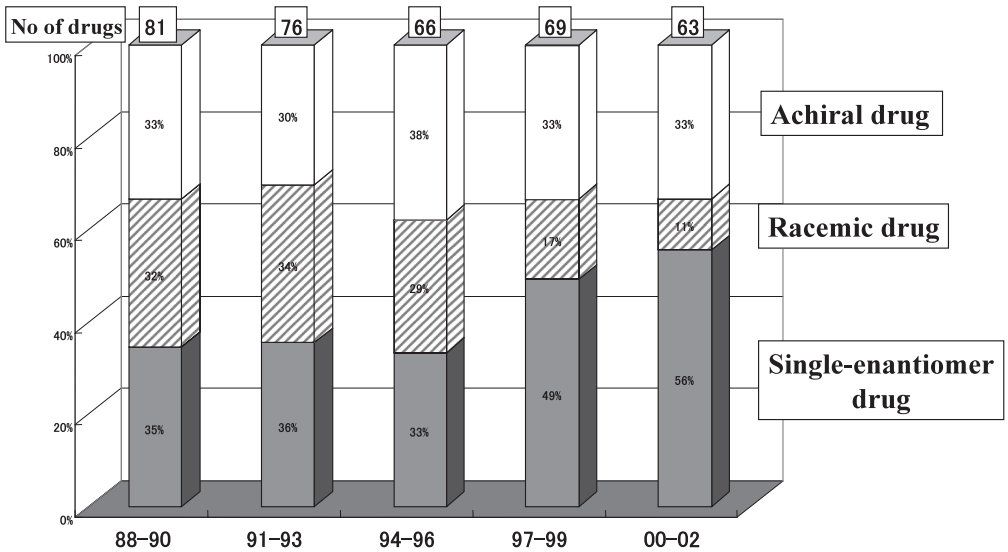

Fig. 1. Number of Drugs Approved in Japan during 1988–2002

The new active ingredients, which are chemical substances and were approved in Japan between 1988 and 2002, were classified according to steric structures.

cal companies and the regulatory authorities, and facilitate development of chiral drugs.

In this article, we analyzed data on manufacturing, quality, pharmacology, toxicology, and pharmacokinetics of single-enantiomer and racemic drugs that were approved by the Japanese government, and discussed the current state of development and approval of chiral drugs.

MATERIALS AND METHODS

The drugs that were approved from January 2001 to July 2003 were surveyed. The information sources were the data summaries [Module 2 of Common Technical Document (CTD) in the present system] that were submitted by the applicants for New Drug Application (NDA) and the approval documentations that were described specifications and test methods of drug substances. This information, especially quality parts, is not completely publicly available, although Module 2 of CTD and review reports available on the Internet.[5,6] Therefore, we did not disclose the individual substances' name.

In this article, the term of 'chiral drug' contains both a single-enantiomer and a racemic drug.

RESULTS

Classification of Approved New Chiral Drugs by Stereochemistry (Fig. 2)

There were 76 new active ingredients that were approved between January 2001 and July 2003 excluding biologics, antiseptics for medical devices and *in vivo* diagnostics.

We classified them into achiral drugs, racemic drugs and single-enantiomer drugs with one-chiral center or multi-chiral centers. The 76 new substances consisted of the 29 achiral drugs (black portion, 39%), the 23 single enantiomer drugs with multi-chiral centers drugs (strip portion, 30%), the 14 single enantiomers with one-chiral center (gray portion, 18%), and the 10 racemic drugs (white portion, 13%). The total number of single enantiomer was 37.

We investigated further details of the 37 single-enantiomer drugs and the 10 racemic drugs as shown in the following sections.

Single-enantiomer Drug Substances

Manufacturing Routes (Fig. 3): The 29 single-enantiomer drugs out of the 37 investigated drugs were produced from single enantiomeric starting materials (gray portion, 78%). In this research, the starting materials indicate starting compounds by manufacturing method in approval documentation and in good manufacturing practices (GMP) compliance.

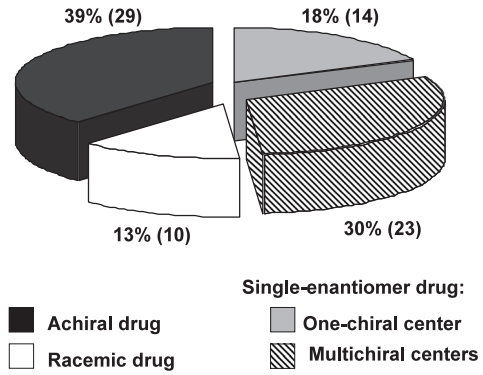

Fig. 2. Classification of New Chemical Drugs by Stereochemistry

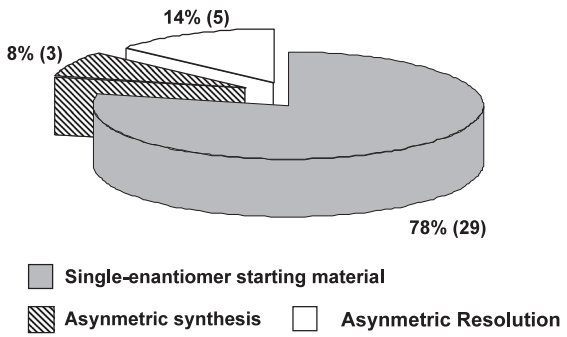

Fig. 3. Manufacturing Routes to Single-enantiomer Drug Substances

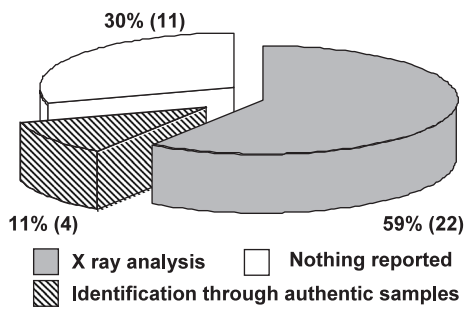

Fig. 4. Stereochemical Characterizations on Chirality of Single-enantiomer Drug Substances

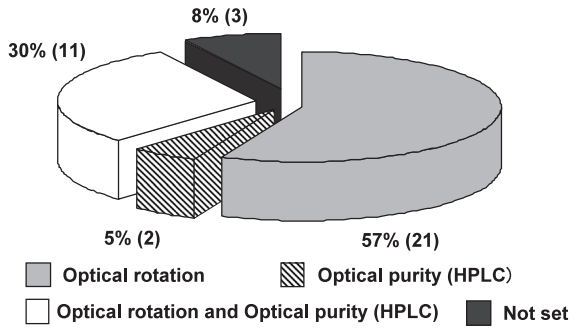

Fig. 5. Specifications for Assuring Chirality of Single-enantiomer Drug Substances

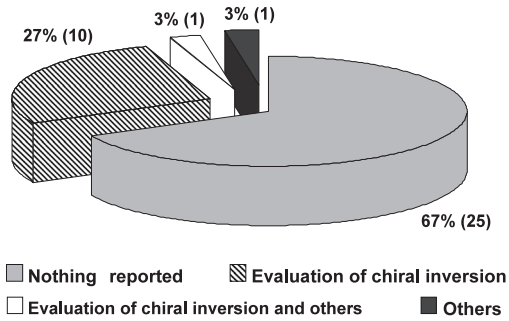

Fig. 6. Pharmacokinetic Studies on Chirality of Single-enantiomer Drug Substances

Asymmetric synthesis was used for formation of single-enantiomers for the three single-enantiomers (stripe portion, 8%).

The five substances were isolated by asymmetric resolution (white portion, 14%). The four substances out of the five were purified by crystallization. The other one was purified by chromatographic resolution.

Stereochemical Characterizations on Chirality (Fig. 4): The stereochemical structures of 22 single-enantiomers were determined by X-ray crystal structure analysis (gray portion, 59%), and 4 single-enantiomers were confirmed by identification through the authentic samples (stripe portion, 11%). No information was reported on characterization of chirality for the remaining 11 single-enantiomers (white portion, 30%).

Specifications for Assuring Chirality (Fig. 5): Optical rotation was adopted as specifications for the 21 single-enantiomers (gray portion, 57%). The chromatographic methods for optical purity determination were chosen for the two enantiomers (strip position, 5%). Both optical rotation and optical purity were adopted as specifications for the 11 enantiomers (white portion, 30%).

No specification for assuring chirality was set for the three enantiomers (black portion, 8%).

Pharmacokinetic Studies on Chirality (Fig. 6): Pharmacokinetic studies were conducted for all of the single-enantiomer drugs, and some sort of pharmacokinetic evaluation relating to chirality was reported for the 12 single-enantiomers. Among them, chiral inversion was evaluated for the 10 single-enantiomers (strip portion, 27%). One out of the 10 single enantiomers indicated chiral inversion on

mouse, although the other 9 single enantiomers did not show any chiral inversion.

One of the other two single enantiomers was proved to generate an enantiomer-specific metabolite (black portion, 3%); and the other one, which did not show any chiral inversions, was additionally investigated on the chiral inversion in metabolite formation (white portion, 3%).

No pharmacokinetic study on chirality was reported in the data summaries of the 25 single-enantiomers (gray portion, 67%).

Racemic Drug Substances

Stereochemical Characterization (Fig. 7): All of the 10 racemic drugs were confirmed to be a racemic substance by some methods. Optical rotation was reported for all of the 10 racemates. Chiral HPLC analysis and X-ray analysis was reported for the nine and the four racemates, respectively. For the four racemate, both chiral HPLC analysis and X-ray analysis were performed.

Pharmacology of Individual Isomers (Fig. 8): Pharmacological activity of each enantiomer was investigated for all of the 10 racemic drugs. Little difference was observed in pharmacological activities of both enantiomers in the five racemates (stripe portion, 50%). For the four racemates, each enantiomer in the racemate indicated different pharmacological potency (gray portion, 40%). For the three of the four racemates, the enantiomers that had greater pharmacological potency were more toxic. The mechanisms of toxicities were same as those of pharmacological activities. In the other racemate, the one enantiomer indicated equivalent toxic potency to the racemate.

Different results were observed between both enantiomers depending on assay systems for the one racemate (white portion, 10%). *In vivo* assay the component isomers in this racemate did not show much difference.

Single-dose Toxicity of Individual Isomers (Fig. 9): Individual single-dose toxicity was reported for 7 drugs out of the 10 racemic drugs. For the three racemates, both enantiomers indicated different single-dose toxicity (gray portion, 30%), and the enantiomer that had higher pharmacological activity was more toxic. Therefore, the development of single-enantiomer drugs was not necessarily beneficial in terms of both safety and efficacy, and the applicants developed the drugs as racemates.

For the four racemates, the individual enantiomers were not different at single-dose toxicity

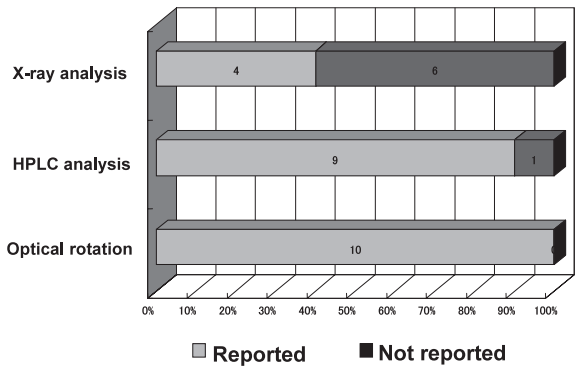

Fig. 7. Stereochemical Characterizations on Chirality of Racemic Drug Substances

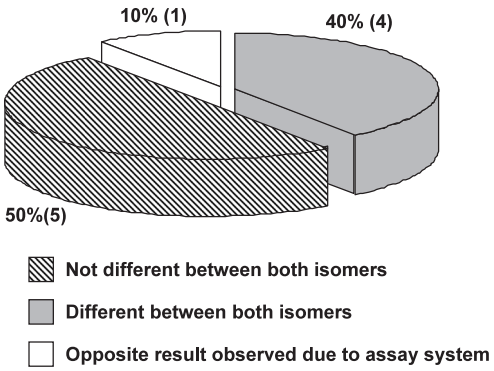

Fig. 8. Pharmacology of Individual Isomers in Racemic Drugs

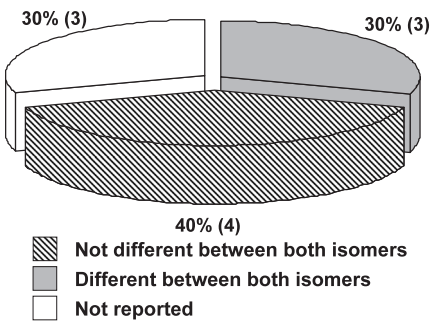

Fig. 9. Single-dose Toxicity of Individual Isomers in Racemic Drugs

(stripe portion, 40%).

Both enantiomers in the three racemates, which had no toxic information of individual isomers, indicated similar pharmacological activities.

Pharmacokinetic Study of Individual Isomers (Fig. 10): Pharmacokinetic evaluations of individual enantiomers were performed for nine racemates using experimental animals and/or human including human tissue-derived materials (Fig. 10). Chiral in-

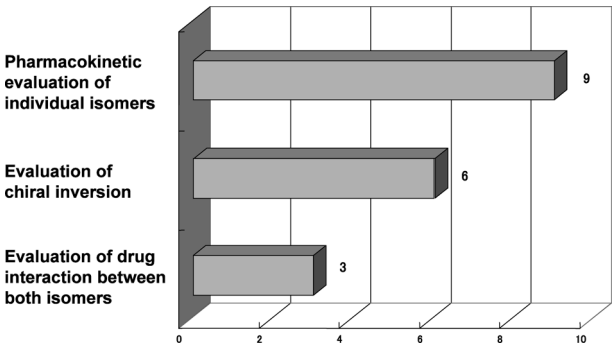

Fig. 10. Classification of Pharmacokinetic Studies on Chirality of Racemic Drugs

version was evaluated for the six racemates, all of which were not observed any chiral inversion. Drug interaction between both enantiomers of the three racemic drugs was investigated. In the other one racemic drug, no pharmacokinetic study relating to chirality was reported.

Pharmacokinetic profiles of enantiomers were investigated for the eight racemic drugs using experimental animals. The four racemic drugs indicated that the individual enantiomers have different profiles. However, there was no difference between both isomers in the rest of four racemates.

Pharmacokinetics was studied using human (healthy volunteers, human tissue-derived materials) for the seven racemates. Pharmacokinetic profiles were different between both enantiomers of the three racemic drugs. The enantiomers of the racemic drug demonstrated different results depending on experimental subjects.

For the four racemates of which each enantiomer indicated different pharmacological potency, both pharmacokinetic profiles of individual enantiomers and chiral inversion were investigated. Drug interaction between both enantiomers was evaluated in the two racemates out of the four.

DISCUSSIONS

Development of single-enantiomer drugs was made possible by the introduction of asymmetric synthesis and chiral separation technologies. In addition, the publication of several guidelines dealing with chiral drugs[7–10] encouraged the development of single-enantiomer drugs for pharmaceutical manufacturers. The following problems of racemic drugs were parts of the reason for making those guidelines:[7–9] One member of an enantiomeric pair might be pharmacologically active and the other inactive; Enantiomers might have different concentration-response relationships for some property; Enantiomers might have completely different activities; Toxicity of a racemic drug might be linked to one member of enantiomeric pairs; Enantiomers might have different pharmacokinetic behavior.

North America[7, 8] and Europe[9] have their original guidelines on chirality that describe manufacturing, quality, pharmacology, toxicology, pharmacokinetics and so on. Additionally, quality of chiral drugs was stipulated by a guideline of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical Human Use (ICH). The guideline, entitled "Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances"[10] and encoded as Q6A, recommends applicants, in case of development of single-enantiomer drugs, to consider the other enantiomer as an impurity and to set the identity tests capable of distinguishing both enantiomers and the racemic mixture.

Japan has not issued specific guidelines on the development of chiral drugs. ICH-Q6A was implemented officially in Japan on May 1, 2001 and came into effect on July 1, 2001.[11] There was a transitional period from the previous guideline until July 1, 2003. Although the drugs surveyed in this paper are not necessarily objects of ICH-Q6A, applicants could prepare to follow ICH-Q6A since it reached Step 4 in October 1999. Additionally, the Japanese regulatory authorities indicated that where the active ingredient is an optical isomer, a method of discriminating between enantiomers should be investigated and the ratio of enantiomers determined.[12–15] Except for the quality point of view, 'Guidelines on Non-clinical Pharmacokinetic Studies'[16] says that when the investigational substance is a racemate, sponsors should monitor the enantiomers individually to determine the pharmacokinetic profiles. The developments of chiral drugs in Japan must be affected by U.S.A. and/or EU guidelines because pharmaceutical developments parallel in worldwide.

The above guidelines do not prescribe a selection strategy to develop as a single enantiomer or a racemate. However, applicants would be expected to provide a scientifically based justification when a racemic drug had been developed instead of a single-enantiomer drug.

Single-enantiomer Drug Substances

For the 11 single-enantiomers, the stereochemical characterization was not reported (Fig. 4). It does not necessarily mean that the Japanese authorities did not receive any information, but it means that no stereochemical characterization was described in the data summaries. In Japan, reviewers use data summaries as a primary assessment document and technical reports as an additional tool, because significant issues are described in data summaries in the Japanese review system. On the other hand, reviewers directly assess individual technical reports on chemistry, manufacturing and control (CMC) in U.S.A.

The stereochemical characterization was reported for all the substances which were produced by asymmetric synthesis or asymmetric resolution, and hence we supposed that the stereochemical characterizations of the 11 single-enantiomers were regarded as less significant for the following reason: Those 11 substances were synthesized from single-enantiomeric starting materials containing multi-chiral centers such as sugars and steroids; Synthetic procedures of those substances were regarded as ensuring their stereochemistry.

ICH-Q6A guideline says that the identity tests should be capable of distinguishing both enantiomers and the racemic mixture for a drug substance developed as a single enantiomer. However, the specification for assuring chirality was not adopted for the three single-enantiomer drugs. One of them had one-chiral center, and the others had multi-chiral centers. Although the reason for rejected specifications is not clear from the data summaries, it might result from the fact that the NDA of three drugs were submitted during the transitional period for implementing Q6A, or those three substances might be regarded as retaining their starting material chirality, or the specification for assuring chirality might be considered to be meaningless.

Also, no pharmacokinetic study on chirality was reported in the data summaries of the 25 (67%) single enantiomers (Fig. 6), 19 of which had multi-chiral centers. In contrast, the chiral inversion was reported for the four single enantiomers with multi-chiral centers, however, less or equal two chiral centers were investigated in those enantiomers. For the single enantiomer with multi-chiral centers, their chiral inversion and isomer-specific metabolism tended to be considered to be complicated and unimportant.

Racemic Drug Substances

Based on the guidelines, we reassessed the justifications for developing the 10 racemates rather than a single enantiomer.

The pharmacologic activity and the pharmacokinetic profile of the individual enantiomers should be characterized, because rapid interconversion *in vivo* was not observed for all of the 10 racemic drugs. Although the principal pharmacological activity was characterized for the individual isomers of the 10 racemic drugs, the pharmacokinetic profiles of the individual enantiomers were not reported for the one. It might be one of the reasons for not reporting that this racemic drug has been a common therapeutic agent for long time in worldwide.

According to the guidelines, it is ordinarily sufficient to carry out toxicity studies on the racemate. The toxicity study of each isomer was not reported for the three racemic drugs, because both enantiomers of these three racemates indicated similar pharmacological activities.

Relating to stereochemical characterization, it is recommended to perform chromatographic tests in addition to optical rotatory tests for mixtures of optical isomers. The chiral HPLC analysis was not performed for the one racemic drug. This racemic drug has been a common therapeutic agent for long time in worldwide, and the Japanese authorities did not require additional stereochemical characterization.

In conclusion, the trend in the Japanese pharmaceutical development is increasingly moving toward the development of single isomers rather than racemates. The chiral development approaches approved in Japan were essentially consistent with the approaches recommended by the guidelines. The racemic drugs, which shared only 13% in the new chemical drug substances, had some rationale to be developed as racemates. Decline of racemic drugs development may continue in Japan as well as worldwide, because some studies need to be carried out with not only a racemic mixture but its component enantiomers.

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REFERENCES

1) The United States Adopted Names (USAN) Council in The American Medical Association (AMA) (2005) *Geometric isomerism and chirality: The USAN perspective*, http://www.ama-assn.org/ama/pub/category/15698.html
2) Stinson, S. (1998) Counting on chirality. *Chem. Eng. News*, **76(38)**, 83–104.
3) Rouhi, A. M. (2003) Chiral business. *Chem. Eng. News*, **81(18)**, 45–55.
4) Ministry of Health, Labour and Welfare (1961) *Enforcement Regulations of the Pharmaceutical Affairs Law*, Article 38, http://law.e-gov.go.jp/htmldata/S36/S36F03601000001.html
5) Pharmaceuticals and Medical Devices Agency (April 2001–present) *Information for approved drugs in Japan*, http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html
6) Pharmaceuticals and Medical Devices Agency (September 1999–October 2005) *Information for approved drugs in Japan*, http://www.jpec.or.jp/contents/c01/link.html
7) Food and Drug Administration (1992) FDA's policy statement for the development of new stereoisomeric drugs. *US Food and Drug Administration regulatory guidance*, http://www.fda.gov/cder/guidance/stereo.htm
8) Health Canada (2000) Stereochemical issues in chiral drug development. *Health Canada guidance document*, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/stereo_e.html
9) European Medicines Agency (1997) *Investigation of chiral active substances European Union Guidelines*, http://www.emea.europa.eu/pdfs/human/qwp/3cc29aen.pdf
10) International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical Human Use (1999) *Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*, Q6A, Step 4, ICH, http://www.ich.org/cache/compo/363-272-1.html#Q6A
11) Ministry of Health, Labour and Welfare (2001) *Setting of Specifications and Test Methods of New Drugs*, Notification No.568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001, http://www.pmda.go.jp/ich/q/q6a_01_5_1.pdf
12) Ministry of Health and Welfare (1994) *Guidelines for Establishment of Specifications and Test Methods for New Drugs*, Notification No. 586 of the Pharmaceuticals and Cosmetics Division, PAB dated September 1, 1994.
13) Branch, S. K. (2001) International regulation of chiral drugs. In *Chiral Separation Techniques. A Practical Approach*, 2nd Edition (Subramanian, G., Ed.) Wiley-VCH, Weinheim, pp. 319–342.
14) Shindo, H. and Caldwell, J. (1995) Development of chiral drugs in Japan: an update on regulatory and industrial opinion. *Chirality*, **7**, 349–352.
15) Shindo, H. and Caldwell, J. (1991) Regulatory aspects of the development of chiral drugs in Japan: a status report. *Chirality*, **3**, 91–93.
16) Ministry of Health, Labour and Welfare (1998) *Guidelines on Non-clinical Pharmacokinetic Studies*, Notification No. 496 of the Evaluation and Licensing Division, PMSB dated June 26, 1998, http://www.nihs.go.jp/mhlw/tuuchi/1998/980626/980626.pdf