Clinical pharmacologists and drug regulation—future perspective in Japan

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- 1 The Japanese pharmaceutical administration system, and recommendations for the improvement of clinical trial methodology following the implementation of GCP guidelines in Japan are described with special reference to three recent developments in Japanese drug regulation.
- 2 The implementation of GCP guidelines has not been fully satisfactory and clinical trials in Japan still run into problems. The Ministry of Health and Welfare has recently established a Committee on Safety of Medicines after serious trouble with a new drug was experienced. The Committee released an interim report on the reform of clinical trials supervision and the system for examination of New Drug Applications.
- 3 ICH-GCP guidelines will be implemented in Japan in the next few years. The principal differences between Japanese GCP and ICH-GCP guidelines, and their effects on clinical trials in Japan with reference to the acceptability of ICH-GCP, are discussed.
- 4 The final proposals on the National Health Insurance drug pricing method and the appropriate use of drugs by the Central Social Insurance Medical Council are anticipated to have a significant impact on the drug market. The changes in pricing system, especially premiums for innovative drugs, and the implications for the drug market are considered.
- 5 In these changed circumstances, the importance of the role of clinical pharmacologists in the framework of the new drug regulations in Japan is reviewed.

Keywords drug regulation in Japan new drug application (NDA) clinical trials good clinical practice (GCP) guidelines International conference on harmonization (ICH) ICH-GCP national health insurance (NHI) NHI drug tariff NHI drug pricing system

Introduction

We have recently published a paper discussing our analysis of the differences between the UK and Japan in the use of standard drugs [1]. We demonstrated major differences in the sales volume of leading drugs in the two countries and tried to account for the differences in terms of clinical trial methodology and local circumstances. We concluded that the reason for these differences lies partly in the process of drug evaluation and partly in the method of drug reimbursement. We anticipated improvements in clinical trial methodology after good clinical practice (GCP) guide-

lines were implemented in Japan for the first time in October 1990. The method of drug reimbursement may now be a more important factor in explaining the differences between pharmaceutical markets.

Three major events occurred during November and December 1995, each of which will undoubtedly have an impact on Japanese drug regulation and the market in the future. Firstly, the Committee on Safety of Medicines released an interim report on the reform of clinical trials supervision and the examination of New Drug Applications (NDA) on 16 November [2]. Secondly, the Central Social Insurance Medical Council or 'Chuikyo' reported its final proposals on the National

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Health Insurance (NHI) drug pricing schedule and the appropriate use of drugs on 22 November [3]. Thirdly, from 29 November to 1 December, the Third International Conference on Harmonization (ICH3) was held in Yokohama, where ICH-GCP (draft ICH tripartite guidelines) and other topics were discussed, and efforts were made to further encourage harmonization around the world [4].

In this paper, I describe the modified perspective of drug regulation and market in Japan, and discuss the potential role of clinical pharmacologists in the future framework.

Mechanism of pharmaceutical administration and manufacturing approval of drugs in Japan

The procedures for application for approval and licence of prescription drugs in Japan are summarized in Figure 1 [5]. The application form is sent for preliminary examination to the appropriate department, either the Pharmaceuticals and Cosmetics Division or the New Drugs Division of the Pharmaceutical Affairs Bureau (PAB), in the Ministry of Health and Welfare (MHW). After reviewing the application, the PAB determines whether a consultation with the Central Pharmaceutical Affairs Council (CPAC) is necessary or not. The CPAC, an advisory organ to the Minister, is comprised of specialists working in public medical and pharmaceutical institutions, and universities. The application first undergoes examination by a subcommittee specializing in the category of the drug for which approval is being sought (e.g. the Subcommittee on Antibiotic Products etc). The subcommittee chairman notifies the applicant of omissions or errors in the application as noted by the subcommittee. The applicant is then given an opportunity to put forward his questions or opinions in reply to the comments of the subcommittee. The application is then subjected to an examination by the competent committee, and finally by the Executive Committee. Approval is only given after all requirements have been satisfied in accordance with the directions of the Executive Committee.

The number of officials engaged in the preliminary examination of the application in the PAB are rather small, approximately fifty, compared with usually several hundred in western countries. The budget allocation, however, does not permit an increase in the number of qualified civil servants in the PAB, even though it is desirable to speed up 'the standard processing period from the receipt of applications to the issuance of approvals' and more importantly, to reinforce the supervision of the NDA. Task sharing between the PAB and the Organization for Adverse Drug Reaction (ADR) Relief, Research & Development (R&D) Promotion and Product Review (Drug Organization) was recently proposed in order to overcome the shortage of staff in supervising the NDA. This proposal will be discussed later. Most of the officials in charge of the NDA examination in the PAB are the pharmacists or chemists. Only 7 out of 140 medical doctors working for the

MHW are in the PAB and few are experts in Clinical Pharmacology. A potential alternative to an increase in staff is to increase the number of officials with medical backgrounds, especially in Clinical Pharmacology.

Recommendations for the improvement of clinical trial methodology in Japan

The implementation of GCP guidelines in Japan

It is important for the applicant to consistently use standard procedures in the tests to be conducted for collecting data. These are also essential for the reliable evaluation of drugs. Guidelines have been worked out in Japan for the different stages of testing (Good Manufacturing Practices: GMP, Good Laboratory Practices: GLP, Good Clinical Practices: GCP, and Good Post-Marketing Surveillance Practices: GPMSP). GCP guidelines (J-GCP) have been enforced since 1990 to establish basic rules for hospitals, researchers and drug companies engaged in clinical trials and were expected to ensure clinical trials of high standards. Five years after the implementation of GCP guidelines, however, some problems still exist in the clinical trials conducted in Japan, examples of which were pointed out following GCP inspections carried out since 1992.

Problems in clinical trials pointed out on GCP inspection

According to article 25 of GCP guidelines, any records related to NDA and required to be preserved by the guidelines, are to undergo GCP inspection if requested [6]. Targets for the inspection should be selected randomly. In 1994, forty-one pharmaceutical companies and 77 medical institutions (26 public and 51 private hospitals or universities) were inspected by the four inspectors, two of whom worked for the PAB and two for the Drug Organization. Only one of them, working for the PAB, was a medical doctor.

I summarize herein the defects or errors which have been pointed out during the inspections in order to show how well the GCP guidelines have worked out and clinical trial methodology has been improved in Japan. Trial subjects were informed of the purpose and outline of the trial and consented in almost all cases, although there was a gap in perception between patients and doctors regarding whether the patients were fully informed [7]. Under the current J-GCP guidelines, consent should be obtained either in written form or orally, and the investigator should make a record in the case of oral consent (article 17 in J-GCP). The latter method occasionally posed problems during the follow up inspection. Monitoring of the trials by the sponsor in general seems inadequate since the investigators control the trial and the sponsors do not have enough experienced staff to visit the large number of centers usually involved in trials. Actually, J-GCP does not require direct monitoring of each case by the sponsor; this is one of the principal differences from ICH-GCP.

Figure 1 Procedures for application for approval and licence of drugs in Japan. Note: (2) to (5) are the procedures for approval of new drugs [5].

The sponsors have been requested to strengthen their auditing function, and the investigators should be sufficiently acquainted with the guidelines, since some errors seemed to be due to their ignorance of J-GCP and the procedures necessary for developing medicines.

The interim report on the reforms in the supervision of clinical trials and the examination of NDA by the Committee on Safety of Medicines

The implementation of J-GCP has not been fully satisfactory and there are still problems with clinical trials in Japan as described above. In 1993, serious

trouble with a new anti-viral agent, sorivudine, occurred in Japan just after its launch. Sorivudine was approved for the treatment of herpes zoster, which is often complicated by cancer and concomitant chemotherapy, and was launched in September, 1993. Fifteen patients who were administered sorivudine and 5-fluorouracil (5-FU) derivatives died of severe neutropenia between September and November because a principal metabolite of sorivudine, bromovinyl uracil, irreversibly inhibits the catabolism of 5-FU [8]. The factors relevant to this tragedy include failure of the system to check for the interactions between drugs, not telling patients the truth about their illness in the case of cancer, and lack of consultation between doctors regarding appropriate

medication for their patients. These problems originate, because of the deficiencies in the Japanese system of collating and disseminating drug information [9], and also in part from flaws in the clinical trial methodology and the NDA examination process.

Hence the MHW organized the Committee on Safety of Medicines in October 1994 to determine (1) how clinical trials should be organized and supervised, (2) how the NDA should be regulated and the process for approval of new drugs, and (3) how post-marketing drug information should be collated. After 12 months of deliberations, on 16 November 1995, an interim report was released on the most urgent subjects, i.e. improving the supervision of clinical trials, and the examination of the NDA. The report stressed that sponsors and investigators must abide by the GCP guidelines more strictly, and proposed reinforcement of the GCP inspection i.e. expansion of the MHW, including an increase in the number qualified officials; improvement of data bases and dissemination of drug information, and supervision by a third party of the NDA. As for a third party, they concluded that the Organization for ADR Relief, R & D Promotion and Product Review (Drug Organization) should supervise the NDA, after being reorganized and reinforced. The principal concept of their recommendations is 'task sharing' between the PAB and the Drug Organization in supervising the NDA and clinical trials so that the PAB concentrates more efficiently on the evaluation of medicines, makes decisions of high quality and shortens 'the standard processing period.' As shown in Figure 2, further responsibility is allocated to the Drug

Organization, in addition to review of an NDA and GCP inspections. This consists of consultation concerning clinical trials (especially about protocol) and thereby an improvement in the quality of clinical trials is expected. The Drug Organization works under the supervision of, or reports to, the PAB and shares tasks with them. Consultation concerning clinical trials and preliminary examination of an NDA are the main responsibilities of the Drug Organization, as are reviews of ordinary drugs and generics, while reviews and inspections for breakthrough and orphan drugs are the PAB's responsibilities. The Committee on Safety of Medicines continues its discussions on the basic concept of clinical trials and ethical issues, greater responsibilities for the sponsor, reconsideration of the chief investigator's role, preparation of ground rules for medical institutions and the protection of human rights e.g. issues of informed consent. The Committee will submit its final report in January, 1996, when the Pharmaceutical Affairs Law will be amended to establish the future framework of Drug Regulations.

International harmonization of drug regulations

ICH-GCP

The US Food and Drug Administration (FDA), the European Commission-European Union (EU), the Ministry of Health and Welfare of Japan (MHW), and the pharmaceutical associations in the three ICH regions

Figure 2 Interim proposal for task share between the Pharmaceutical Affairs Bureau (PAB) and Organization for ADR Relief, R&D Promotion and Product Review (Drug Organization) in supervising clinical trials by the Committee on Safety of Medicines. ADR: Adverse drug reaction, IRB: Institutional review board, IEC: Independent ethical committee.

have cooperated with each other in order to promote the harmonization of technical requirements for the registration of new drugs based on the ICH objective, which is to introduce efficiently and promptly high-quality, efficacious and safe drugs to patients around the world. ICH discussions and recommendations have been presented in fora, resulting in ICH1 in Brussels (1991), ICH2 in Orlando (1993) and ICH3 in Yokohama, Japan, 29 November to 1 December 1995.

ICH-GCP guidelines are to be signed by the three regulatory parties to ICH at the Steering Committee Meeting in May 1996 and then will be recommended for adoption to the respective regulatory bodies. Thus, it is important to review the principal differences between current J-GCP guidelines and those of ICH-GCP, as shown in Table 1, since the latter will be implemented in 3 to 5 years time and will undoubtedly have a considerable effect on the conduct of clinical trials and operations of

pharmaceutical companies in Japan. In the current Japanese system, the chief investigator controls a clinical trial, whereas there is no chief investigator but coordinating investigator(s) with limited responsibilities in the ICH-GCP guidelines. The chief investigator organizes a research group consisting of a subcommittee and investigators. He is responsible for preparation of the protocol and the study report and supervises all the activities in the trial in J-GCP. Most of these responsibilities should be assumed by the sponsor in ICH-GCP and will pose for the pharmaceutical industries problems such as selection of competent investigators, preparation of the protocol and study report, and effective implementation of monitoring. On the investigators' side, they might feel embarrassed by close monitoring by the sponsor and inspection by the regulatory authorities under the ICH-GCP guidelines since the supervision of the clinical trial will be reinforced. The subjects of the trials might also

Table 1 Principal differences between current Japanese GCP (J-GCP) and ICH-GCP

<i>Current J-GCP</i>	<i>ICH-GCP</i>
<i>Sponsor's responsibilities</i>	
1. The appointment of chief investigator	1. Quality-assurance, management, monitoring and auditing of the clinical trial
2. Providing investigators and chief investigator with information about efficacy and adverse reaction of the test drug	2. Investigator selection
3. In-house auditing	3. Preparation of protocol and study report
<i>Chief investigator's responsibilities</i>	
1. Preparation of protocol and study report	<i>No chief investigator</i> (Coordinating investigator)
2. Supervision of the clinical trial	Responsibilities should be discussed with the sponsor and put in writing in advance of the clinical trial
3. Instruction to investigators	
4. Transmission of information from the sponsor to investigators	
<i>Investigator's responsibilities</i>	
1. ADR report to the head of institution and chief investigator	1. Should accept monitoring and auditing by the sponsor, and inspection by the regulatory authorities
2. Case report form to chief investigator	2. ADR report to the sponsor and IRB/IEC
<i>Institutional Review Board/Independent Ethics Committee (IRB/IEC)</i>	
1. Members of IRB collectively have the qualification and experience to review the trials and do not necessarily include a member who is independent of the trial site	1. Should safeguard the rights, safety, and well-being of all trial subjects
2. Reviewing occasional progress reports but not ADR reports	2. Should include at least one member who is independent of the trial site
	3. Should consider the qualification of the investigator for the trial
	4. Should review both the payment to subjects and rewards for investigators
	5. Reviewing all serious and unexpected ADR reports in addition to progress reports
<i>Medical institution's responsibilities</i>	
1. Making a contract with the sponsor	Should take responsibilities for investigators if required by the law
2. Organizing IRB/IEC	
3. Should approve conducting the trial or recommend modification according to the views of IRB	
4. Giving instructions to investigators	
<i>Informed consent</i>	
Written or oral consent	Written consent

feel embarrassed if they are always asked for written consent since the concept of 'informed consent' is less well understood in Japan than in Europe and US. Most importantly, the investigators must be well acquainted with ICH-GCP guidelines in order to be able to accept any proposed changes in the clinical trials, otherwise the adoption of new guidelines may result in 'emptying Japan of clinical trials.' It has been alleged from the industrial side that clinical trials have not progressed well since the implementation of J-GCP guidelines, and that trials could be carried out better abroad in the future. On the positive side, however, it could prevent a flood of poor clinical trials and ensure clinical trial of a high standard (in distinguished medical institutions) in Japan.

Future of the pharmaceutical industry under the ICH-GCP

The implementation of ICH-GCP may accelerate the selection of more competent pharmaceutical companies, since smaller companies cannot easily conduct clinical trials because of greater responsibilities and risks for the sponsor. It will also become more difficult to make a profit by launching me-too drugs. Research and development activities of a high standard may determine the survival of a company and Contract Research Organizations (CRO) may play a more important role in conducting clinical trials in the future. Another expectation, and the most threatening to the domestic pharmaceutical industry, is that the international pharmaceutical giants may increase their market share in Japan since foreign clinical data will be acceptable to the Japanese regulatory authorities. ICH-GCP will also accelerate the internationalization of domestic companies since they will have no obstacles to developing a breakthrough drug worldwide if they are really competitive.

To meet the requirements of the ICH-GCP guidelines, the training of physicians is of primary importance, including the registration of competent investigators. These well-trained and qualified physicians should be in charge of clinical trials both in medical institutions and the pharmaceutical industry. Pharmaceutical companies must harness specialists to prepare protocols and study reports themselves, and to monitor the trials in accordance with the new guidelines. The activities of CRO in Japan are still limited and their acceptability is now under consideration. Nevertheless, it is expected that they will soon be officially recognized and will play an important role in the development of drugs in the future.

National health insurance (NHI) drug tariff in Japan

NHI drug pricing system in Japan

The NHI Drug Tariff has not been merely the price list to reimburse drug expenses to doctors, it is also an expression of the government's policy to encourage the pharmaceutical industry to grow in Japan, and has

worked successfully, resulting in one of the three largest drug markets in the world and a dozen pharmaceutical companies of high reputation. The NHI Drug Pricing System is opaque to outsiders and often becomes a target for criticism, especially since containment of the cost of National Health Care is an imperative issue for most developed countries. Generally speaking, the NHI drug price is determined by analogy with the mean price of comparable drugs, with or without premiums, depending upon the advantages of the new drug, or less frequently, on the summation of direct and indirect costs to the manufacturer and distributor.

As shown in Figure 3, the NHI Drug Price is reduced every 2 years according to the Tariff Rate Calculation to reflect actual market prices, leaving a margin for the pharmacy or doctor who dispenses the drug. The margin, called the reasonable zone (R-zone), was reduced from 15% in 1992 to 13% in 1994 and will be reduced to 11% and 10% in 1996 and 1998, respectively. Since general practitioners often dispense their prescribed medicines themselves in Japan, and drug price differentials used to be larger, the use of drugs may have been biased [1]. If this is the case, this unusual situation should be analyzed in-depth before any revision of the drug pricing system, although the reduction in drug prices has provided the main financial resources for revising (increasing) fees for medical procedures. There is a special repricing-programme for a drug for which the indications are extended, and consequently the sales volume increased, or showing a markedly higher sales volume than expected following its launch. For example, interferon underwent repricing after its use had been extended to the treatment of chronic active viral hepatitis.

Discussions at the subcommittee of the Central Social Insurance Medical Council on the NHI drug prices and the appropriate use of drugs

As our society ages, Health Insurance financing becomes more difficult. After the shock of the economic bubble, it is not possible to increase insurance premiums in line with costs and the reduction of drug prices is again a target for managing resources. Therefore, the Central Social Insurance Medical Council (or 'Chuikyo') established a subcommittee in November 1994 to discuss the NHI drug pricing system and the appropriate use of drugs. There has been criticism of the high ratio of drug expenses to total medical expenditure in Japan and the high profitability of pharmaceutical companies. Some doctors also agree with the reduction of NHI Drug Prices, and lobbied for an increase in consulting fees, partly because separation of dispensing from prescribing is increasing, and partly because drug price differentials have shrunk as drug companies have increased Invoice Prices. However, there is concern that cost curtailment may result in a decrease in the quality of medical care if it is merely driven from the revenue side without a careful consideration of the appropriate use of drugs. Radical reform of the drug pricing system reduces the enthusiasm of pharmaceutical companies for developing

Figure 3 National Health Insurance (NHI) Drug Tariff in Japan—Constituents of the NHI Drug Price—*NHI Drug Price is to be reduced every 2 years according to Tariff Rate Calculations as follows: New NHI Drug Price = Weighed average actual market price + Reasonable zone (R zone) **R-zone has been reduced from 15% of NHI Drug Price in 1992 to 13% in 1994. It will be further reduced to 11% and 10% in 1996 and 1998, respectively. ***The drug price differentials between actual market price and NHI Drug Price have been (or at least used to be) the major component of hospitals' and general practitioners' income.

breakthrough drugs, resulting in little or no innovation in medication and an increase in the total cost of health care in the long run. We should discuss the expense of drugs in terms of total cost of treatment and be aware that the appropriate use of innovative drugs is most cost-effective.

The final proposal on the NHI drug pricing system by the Central Social Insurance Medical Council

After discussing the draft proposal both internally and with the pharmaceutical industry, Chuikyo reported the final proposals on the NHI drug pricing method and the appropriate use of drugs on 22 November 1995 [3]. In the proposal, premiums for new drugs were increased to help offset the high cost of developing drugs with significant medical advantages, and the pricing of new drugs with little or no medical advantage was made less favourable as shown in Table 2. Repricing rules for some existing drugs were modified and will be implemented in the fiscal year 1996. The price of generic drugs was

reduced from 90% to 80% of the branded original and the price will be adjusted if it is significantly different from the foreign price (more than twice or less than half). Chuikyo also recommended that medical institutions should be allowed to choose either flat sum payment or fee-for-service in in-patient care for the aged, outpatient care for the aged or children, and also surgery. The final decision on the extent of the choice will be made by the government when the budget for 1996 is finalized. In addition, Chuikyo clarified the allocation of the cost of clinical trials to the sponsor under the health insurance scheme, and proposed more appropriate use of drugs.

Chuikyo and its subcommittee continue to explore various issues such as whether to continue the current NHI Drug Price Tariff or not, pricing of long-term listed drugs, and how to raise patients' consciousness of the cost of health care, cost-benefit analysis methodology, appropriate drug use for aged patients and promotion of the separation of dispensing from prescribing. The pharmaceutical industry is most concerned with the pricing of long-term listed drugs which was

Table 2 The final proposal on the NHI drug pricing method by the Central Social Insurance Medical Council-Premiums in new drug pricing

Current system	Revised system
	<i>Premiums for innovation*</i>
A. Breakthrough drugs**: 10–30%§ (20% as the standard)	A. Breakthrough drugs: 20–60%§ (40% as the standard)
B. New drugs with medical advantages: 1.5–4.5§ (3% as the standard)	B1. New drugs with medical advantages***: 5–15%§ (10% as the standard)
C. Other new drugs: No premiums (Analogue with the mean price of the recent comparable drugs)	B2. New drugs with a medical advantage#: 1.5–4.5%§ (3% as the standard)
	C. Other new drugs: No premiums (Analogue with the mean price of comparable drugs launched in the previous 10 years)
	<i>Premiums for market potential</i>
A. New drugs with a limited number of patients: 1.5–4.5%§ (3% as the standard)	A1. New drugs, the sales volume of which is expected to be extremely small similar to so-called orphan drugs: 5–15%§ (10% as the standard)
B. Other new drugs: No premiums	A2. New drugs, the market share of which is expected to be similar to comparable drugs and less than 0.5% of the total market: 1.5–4.5%§ (3% as the standard)
	B. Other new drugs: No premiums

*An innovative drug is defined as follows: 1) A breakthrough in research and development. 2) Significant advantage(s) in efficacy or safety compared to existing drugs is demonstrated objectively and scientifically. 3) Revolutionary impacts on the remedy and significant contribution to improve the therapy of the indicated disease are expected.
**Breakthrough drugs should have all three innovative features defined above.
***Drugs with medical advantages should have any two innovative features.
#Drugs with a medical advantage should have any one innovative features.
§Proportional allocation.

reviewed in ‘Memorandum on the Discussion Points’ released in June and further discussions are planned.

Colin Dollery for his guidance and tuition in the field of Clinical Pharmacology and wish him a happy retirement.

Conclusions

Under the new NHI Drug Tariff proposed by Chuikyo, pharmaceutical companies cannot help but develop drugs with medical advantages to survive. The advantages should be demonstrated in clinical trials under the ICH-GCP guidelines which will be adopted in a few years. Clinical pharmacologists or physicians with adequate knowledge of Clinical Pharmacology will play a key role in medical institutions, regulatory authorities and the pharmaceutical industry to conduct strictly controlled evaluation of drugs. In daily medical practice, it will be more important to promote the appropriate use of drugs in terms of efficacy and economy. The real value of a drug should be verified by accumulation of records of each case of medication. More comprehensive analysis of medication practices from the point of view of Pharmacoeconomics or Pharmacoepidemiology using a medical information data base or meta-analysis of clinical trial outcomes may be helpful in establishing the future guidelines for the appropriate use of drugs. The NHI Drug Price Tariff should reflect the outcomes of such analysis.

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