The working group on “Future Postmarketing Surveillance (PMS) in Japan” was established by the board of JSPE in May, 2002.

The working group have had meetings on a monthly basis to discuss issues on “Future PMS in Japan”. The working group worked out the task and prepared a report on this subject.

The report was approved by JSPE, published in the journal of JSPE, “Pharmacoepidemiology 2003; 8: 1-36, and presented in other pages of this website in Japanese.
The following is a provisional translation into English.

Provisional translation of the report of the working group on “Future PMS in Japan”

Translated by Yuka Ohgaki (AstraZeneca Japan),
Fumiko Miyaji and Mikihito Kosuge (Eli Lilly Japan)

Chair of the working group : Yasuo Ohashi (Professor of University of Tokyo)

Members of the working group
Yasuo Arima (RAD-AR Council)
Shigeru Kageyama (Jikei University School of Medicine)
Akira Kamiya (Yamaguchi University)
Shikifumi Kitazawa (Nihon University)
Akira Kokan (RAD-AR Council)
Kiyoshi Kubota (University of Tokyo)
Takeshi Mayama (RAD-AR Council)
Mayumi Mochizuki (Kitasato University)
Takeshi Nakamura (Nihon University)
Toshimichi Nishi (JPMA)
Yutaka Nojima (RAD-AR Council)
Takao Orii (NTT Higashi Nihon Kanto Hospital)
Hironori Sakai (Mitsubishi Pharma Corporation)
Akira Sakuma (The Organization for Pharmaceutical Safety and Research)
Naokata Shimizu (The Organization for Pharmaceutical Safety and Research)
Takashi Shirai (RAD-AR Council)
Hideaki Suzuki (JPMA)
Hiroyuki Usuki (JPMA)
Motoko Watanabe (Pfizer Pharmaceuticals Inc.)
Secretariat: Tadashi Kusunoki (Japanese Society for Pharmacoepidemiology)

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Report from the Working Group on "Future Postmarketing Surveillance（PMS）in Japan"

Preface

Clinical trials for drugs before marketing are studied in the subjects of selected patients, i.e., those clinical trials are conducted in the "ideal world", whereas post-marketing drugs are used in the "real world" and "medical practice", therefore unexpected adverse events and interactions may occur. There have been cases such as SMON due to enteobioform where unexpected adverse drug reaction became social issue. However, as seen in the case of haemorrhagic cerebral stroke with PPA (phenylpropanolamine)[1)], there is a case where causal relationship between an adverse event and a drug was detected[3)], leading to adequate post-marketing studies which contributed to establishment of appropriate use of the drug.
On the other hand, the effect of aspirin on prevention of relapse of cardiac accidents such as myocardial infarction was revealed almost one century after its launch[2)], and the primary effect of diuretics and beta blockers on prevention of cebrovascular/cardiovascular accidents was discovered by post-marketing studies.

All of these facts were found after launch and the importance of post-marketing studies for medical community should be recognized. In order to establish further appropriate drug use, close observation by a physician and well organized post-marketing studies are crucial, while studies by medical institutes and public entities are necessary as well as PMS conducted by pharmaceutical companies. Recently, there have been initiatives to put more emphasis on the post marketing such as introduction of Early Post-marketing Phase Vigilance (EPPV), revision of Pharmaceutical Affairs Law (PAL) including a change from manufacturing to manufacturing marketing approval, PMS as a new theme at ICH. Assuming that the era of new medicine started in the mid 20th century, it seems that interest in the post marketing has eventually begun to increase in the 21st century.

Under the circumstances, JSPE organized 'Working Group on 'Future Post-marketing Surveillance in Japan' where "PMS as it should be in future" has been discussed and compiled into this report. The report reviewed proposals to make PMS further developed and recommendations toward relevant entities. It is hoped that those who are involved in the post marketing vigilance and studies would review and refer to following comments, and would also make feedback.

OVERVIEW

It is possible that PMS (Post-marketing surveillance) has been interpreted as post-marketing surveillance conducted by companies, however, broader concept including post-marketing studies initiated by organizations of researchers and public institutions is adopted here. PMS is necessary for safety surveillance of marketed (ethical) drugs and to add evidence of efficacy. It should be continued as far as the drugs are marketed. Scientific aspects of PMS are mainly discussed but issues concerning its system are also reviewed. In this statement, general issues are discussed while current issues are examined and proposals of measures to resolve/improve are listed in Sections of Detailed Discussion.

(1) Common recognition on necessity of PMS among various sectors

The objective of PMS is to establish appropriate use of drugs. Pharmacotherapy should be selected according to evidence of efficacy/safety indicating whether the drug is appropriate to the target disease and to the target patient, i.e., evidence based medicine (EBM). Because many evidences are obtained after a drug is marketed, PMS is necessary for vigilance of marketed drugs, to foster them to better products, and to establish their appropriate use. There are opportunities for improvement in Japan, considering the current situation as discussed below. It is important, for the issues which are difficult to improve in short term, to make directions for improvement in long term by establishing the ideal situation in the future. As prerequisite for every improvement, companies, health care providers and regulatory authorities should commonly recognize the necessity of PMS and give mutual cooperation.

(2) Initiatives of PMS

The word “PMS” used to mean post-marketing surveillance conducted by companies in compliance with the pharmaceutical regulatory systems. However, many drugs may be compared each other in medical practice and efficacy studies to evaluate concomitant use may be conducted outside of the framework of company, and safety issues common to a therapeutic class may be significantly important in the light of public health. Therefore, PMS initiated not only by companies but also by researchers and public organizations are necessary.

Since such PMS is not adequately carried out under the current condition, it is recommended to enhance support for PMS conducted by organizations outside of companies. It is essential for regulatory authorities, public organizations and companies to provide financial and other supports to develop non-company PMS.

(3) Attitudes of companies

Some companies consider that PMS may be conducted only within the regulatory requirements, and significance of PMS has been neglected compared to the studies before approval.
Under the concept of bringing up better drugs throughout their lifecycle from development to marketing, PMS should be considered more importantly with consistent study objective and personnel training and organization should be improved. Systems to appropriately handle issues after marketing, to support studies conducted outside of companies such as investigator initiated studies, and to disseminate information on appropriate use of drugs to health care providers should be further promoted. Mechanism to assess such activities internally and externally from company should be defined.

(4) Regulatory systems and organizations

ADR/infection reporting, re-examination and re-evaluation are the major regulatory requirements for marketed drugs in Japan. Some revisions have been made including cooperation of ADR reporting not only from designated institutions but also from all institutions, abolishment of 3000 cases of Clinical Experience Investigation (CEI), and establishment of EPPV. While ADR reporting system is similar to that in foreign countries, re-examination and re-evaluation systems do not exist in Western countries. Classification of the investigations such as CEI, Special Investigation (SI) and post-marketing clinical studies conducted by companies are not based on the scientific methodology.

In conformity with ideal PMS in future, it is requested to review the current regulations and organizations and systems to apply the regulations, in consideration of its purpose/function, international harmonization, and distinction between methodology and regulations.

(5) Recognition by health care providers and issues of education

Health care providers not only "provide" but "use" evidences. Appropriate PMS cannot be conducted when health care providers do not consider PMS important, because all PMS data are generated by health care providers. However, health care professionals are less concerned with PMS, and they do not fully understand that Article 77-3 of PAL requires their cooperation. The background to this is that pharmacotherapy has not been considered important in the process of medical/pharmaceutical education. Even if financial support to PMS is increased as stated in (2) above, PMS would not be improved unless people who wish to conduct studies to make evidence increase.

To enhance attention to PMS and to bring up personnel who would achieve improvement of pharmacotherapies, it is requested to further improve education/training/practice of pharmacotherapy during education of health care professionals including physicians, pharmacists, and nurses.

(6) Practical use of pharmacoepidemiology

Evaluation of drugs in medical practice is feasible only with PMS. Clinical studies before marketing are intervention studies with experimental elements. Intervention of patient treatment should be limited as much as possible in PMS and evaluation should be as close as actual medical practice. Studies, in which drug users and patient populations are subjects as they are, are called observational studies. PMS should be based on the pharmacoepidemiology which is epidemiology concerning drugs.

In Section 5 of Detailed Discussion, scientific principle of PMS was examined to determine which study method should be chosen according to the research objective. Methods to verify causal relationship between a drug and an adverse event, methodology of observational studies, and difference between pre-marketing clinical studies and PMS are not adequately understood, and experience of PMS using correct methodology is insufficient. Current issues and measures to improve them are reviewed in Section 5 through 11 of Detailed Discussion. The ideal PMS in the future is recommended with summary of these items as follows:

According to the methodologies compiled in Section 5 of Detailed Discussion, it is desirable to draft in cooperation with related societies "Scientific guideline of PMS" which is common to all types of PMS conducted by companies and organizations outside companies. Followings are considered necessary: system and methodology of PMS should be distinguished, and the method which was designated as CEI should be positioned as one of the methods of observational studies. Data in medical institutions should be archived for research purpose, and observational studies using database should be developed as one of significant PMS methods. Long term and large scale clinical studies to obtain evidence of long term use in Japanese population should be planned and implemented appropriately in accordance with "simple and large" principle. Maintenance of investigation sites in good environment should be facilitated.

(7) Spontaneous reporting and safety surveillance

Important role of PMS is to detect unexpected serious adverse drug reactions (ADRs). It is essential to obtain reports of adverse event (AE) cases or suspected ADR cases. Reports from health care providers include spontaneous reports and solicited reports relating to studies and investigations. They are separated between direct reporting to authorities, and indirect reporting via companies which is called company reporting. All of them are referred to as "spontaneous reports" here in after, but the number of reports has not increased as expected. (See appendix to Section 6 of Detailed Discussion). Causal relationship with drugs has been evaluated in each case, but currently, studies of statistic methods using large accumulated data from spontaneous reports have been initiated globally, and it is called signal detection[4)].

Safety issues are increasing, and it is necessary to promote both quality and quantity of spontaneous reports of ADRs, etc. PMS should not only request companies to enhance AE reporting but also call health care providers' interest. As for signal detection which has significant meaning in safety surveillance, it is proposed to advance methodological studies to utilize data accumulated in regulatory authorities and to create concepts of systems mainly operated by regulatory authorities or their related organizations and systems in which companies and other organizations can share the accumulated data.

(8) Risk/benefit balance and overall evaluation

PMS gradually increases information on the appropriate use of drugs, and balance of safety and efficacy, and economic efficiency are important factors for the evidence of EBM and appropriate use of drugs. Evidence of long term prognosis may affect selection of pharmacotherapy, and safety issues may affect not only life cycle of drugs but life of patients exposed. While it is the most important task of PMS to secure safety, overseas data should be utilized more frequently for the drugs used globally, and safety measures should not be determined only with safety data. Views from patients exposure and from society should become more important for the future since users of the drugs and patients are the ones who suffer from health hazard affecting people around them such as relatives, and it is society that should take risks. When decision on appropriate use of a drug is made, balance of risk and benefit should always be evaluated fairly and objectively and a comprehensive decision by considering type of diseases, necessity in medical practice, estimated patient exposure, similar drugs, economic efficiency and view points from patients and society should be sought. Regulatory authorities and companies must make decision by fulfilling their accountability to their decisions, and must take necessary countermeasures.

(9) Ethical principles

It is obvious that conduct of PMS must be scientifically and ethically appropriate. "Ethical guideline for epidemiological studies" has already been implemented by Ministry of Education, Culture, Sports, Science and Technology (MECSST) and Ministry of Health, Labor and Welfare (MHLW). It has become more important to plan PMS appropriately and to conduct it with thorough consideration of human rights of subjects/patients.

It is recommended to specify ethical principles of PMS in compliance with "Ethical guideline for epidemiological studies" and to prepare "PMS Guideline" according to the scientific principles in (6) above.

Proposals and Requests

The issues discussed in the previous chapter of over view were assessed for current situation, obstructive factors, and direction of improvement, and measures for improvements were reviewed. In this chapter, proposals and requests reached through each section of Detailed Discussion are summarized. In the following chapter discussions on each issue are described.

1. Initiatives of PMS: Overview (2)
There are issues for which non-company organizations should have initiative in research for safety that has social impact and research for efficacy in which series of drugs and drug classes are studied, however, PMS conducted outside of companies has not been implemented adequately.

Measures to increase investigator initiated PMS and public PMS: from Section 1 of Detailed Discussion.
(1) Increase financial support from public organization, companies and other groups to PMS organizations independently of companies, and newly created individual research or research organization. Pooled funds by contribution from companies according to their sales could also be used for this support.
(2) It is desired to support not only R&D but also PMS of drugs with the independent administrative institution to be established by combining the Evaluation Center and the Organization of Pharmaceutical Safety and Research to establish a system to operationally support PMS and to provide PMS with financial support.
(3) It is requested to establish public organization with functions such as selecting research subject for PMS conducted outside of companies, supporting organization and implementation of research, and arrangement of outsourcing and an organization which actually conducts research is included in the future. When possible, it is preferable to incorporate such organization in the independent administrative institution described in (2) above.
(4) It is requested to establish pharmacoepidemiology course to develop human resources such as PMS researcher, PMS coordinator, and research manager in curriculum of National Institute of Public Health, and a one-year postgraduate school of vocational training to be newly established, etc
(5) Orphan diseases and pediatrics are the examples of the area where indications of drugs are expected to be expanded. For such issues, it is requested to establish systems to conduct public research with support from companies as a prerequisite and to aid to research with public funds.
(6) It is desirable that result of investigator initiated PMS is allowed to be a part of re-examination application data and that companies could provide financial support to such PMS by keeping transparency and independence from companies.
(7) Methods, such as revision of health care system, to reflect the evidence of off-label use to medical practice should be sought.

2. Attitudes of Companies: Overview (3)
Pharmaceutical companies must attach importance to PMS by keeping consistency with research projects from development phase to post-marketing phase and take appropriate measures to issues occurring after marketing.

Attitudes required to companies in the future: from Section 2 of Detailed Discussion
(1) PMS should be conducted adequately and issues should be managed in timely manner by stopping conservative attitude of just complying with regulations but assuming constructive approach to promote drugs consistently from pre-marketing to post-marketing to be valuable.
(2) Safety information should be transparent and scientific. Safety issues should be managed promptly with sufficient accountability.
(3) Organization for PMS should be expanded by increasing awareness of importance and necessity of Pharmacoepidemiology, developing human resources and allocating sufficient personnel. There is a proposal to consider establishment of an official certification system by the JSPE for persons in charge of product safety in companies as one of eligibilities for Manufacturing Marketing Supervisor General and Safety Control Manager under the revised PAL.

(4) Assuming PMS conducted outside of company advances as described in Section 1 of Detailed Discussion, companies should contribute fund to supporting organization according to their sales, provide researches independent of companies with drugs and information and provide fair funds.

3. Regulatory systems and organizations: Overviews (4)
It is requested to review regulatory systems and organizations in which the regulations are operated in accordance with the recommendations for future PMS.
Direction of the review: from Section 3 of Detailed Discussion
(1) Systems should be reviewed by considering objective and function, international harmonization and distinction between methodology and regulation.
(2) Consistency between organization and its operational purpose and simplicity of organization should be considered.
(3) Development of people with expertise and neutrality who could permanently be assigned to PMS, and establishment of organization specialized in PMS is desired. Research organization for safety surveillance should also be included in the future.
(4) It is requested that the data at regulatory authority on spontaneous reports including adverse reactions, periodic safety reports, clinical experience investigations and special investigations should be compiled to database in timely manner which is available to companies and other research organizations under certain condition.

4. Recognition by health care providers and issues of education: Overview (5)
Further fulfillment of education and training for pharmacotherapy for physicians, pharmacists and nurses to increase awareness in PMS and to develop people who achieve improvement of pharmacotherapies is required.

Request to bring up talented people: from Section 4 of Detailed Discussion
(1) Not only pharmacological actions of drugs on organs but also drug development process and PMS which is conducted to establish appropriate use should be further incorporated to the undergraduate education for medical students.
(2) The state examination for medical doctor includes only about 30 questions on pharmacotherapies. The answers to most of the questions are to select an appropriate drug according to its pharmacological action. It is recommended to increase questions regarding comprehensive pharmacotherapies including efficacy and safety.
(3) Training and practice for medical school graduates should aim at accumulation of practical experience including methodology for interventional studies and observational studies, EBM, development of pharmaceutical products, and method for assessment of post-marketing efficacy and safety (adverse reaction) with clinical pharmacology, clinical epidemiology and pharmacoepidemiology as major theme.
(4) Concepts in the model curriculum for pharmacy education proposed by the Pharmaceutical Society of Japan in the light of shift to 6-year system should be implemented at early opportunity, and professional education should be enhanced to include pharmacotherapy, methods of clinical research and PMS regulations.

5. Practical use of pharmacoepidemiology: Overview (6)
PMS evaluates drugs in actual practice and it should be based on pharmacoepidemiological methodology.

Observational study or interventional study should be selected according to the research subject illustrated in Fig. 2: from Section 5 of Detailed Discussion
(1) It is recommended to prepare “PMS Guideline” common to PMS conducted by companies and by outside of companies with cooperation from various groups by adding ethical principles in Section 12 of Detailed Discussion to scientific rules in Fig.2 of Section .5 of Detailed Discussion.

It may be difficult to apply Fig 2 in practice, however, effort is necessary to gradually approach to ideal situation in the guideline without compromising with the current condition as much as possible.

The internationally valid term for observational study, “cohort study”, should be applied to CEI. It should be included in the guideline to be developed as useful method of PMS: from Section 8 of Detailed Discussion.

(1) Guideline should stipulate that intervention and selective bias should be avoided in cohort studies, and that control group should be established in the study when possible.
(2) When a company plans a study in which users of other drugs in actual practice are sampled and compared with comparator group, contacting with third party, etc. should be used to establish the mechanism to avoid bias.

Data at medical practice should be compiled into database for utilization for observational studies in PMS: from Section 9 of Detailed Discussion9
(1) Leading body should be established at regulatory authority or related organization, and database should be developed, with financial support, through cooperative system with regulatory authority, health care providers, insured by health insurance, academics and companies.
(2) Maintenance and improvement of database should be conducted by a non-profitable neutral organization with public funds. It should be managed to accept request for access to the database from outside organization including companies.

Following measures other than 1-4 in Section 1 of Detailed Discussion are necessary to develop clinical studies necessary for PMS: from Section 10 of Detailed Discussion

(1) A job position (Clinical study coordinator) which includes management of studies and assurance of data quality should be established. Enhancement of education and development of people should be adequately implemented and qualified people should be assigned to medical institutions to gain their experience.
(2) For long-term and large-scale studies, principle of “simple large” should be applied in plan, implementation, management and analysis. Operation should be standardized especially for quality assurance and audit by taking balance of cost into consideration and by putting emphasis on primary endpoints, important baseline parameters and mandatory data relating to serious adverse reactions, etc.

6. Spontaneous reporting of ADR and safety surveillance: Overview (7)
Issues concerning safety have been increasing, and safety surveillance system should be reviewed by promoting quality and quantity of spontaneous reporting of ADR and by evaluating international trends.

Measures to promote quality and quantity of spontaneous reports: from Section 6 of Detailed Discussion

(1) The Pharmaceutical Affairs Law revised in 2002 obligates health care professionals to conduct spontaneous reporting according to Article 77-4-2, Item 2. This should be communicated in order to promote understanding of the requirement by the relevant people.
(2) Reporting formats for direct reporting from health care professionals and for company reporting should be standardized and simplified. Health care professionals and company personnel should be educated on what and how to report. Importance of reporting of serious cases and unexpected adverse reactions should be emphasized.
(3) Direct reporting usually comes from physicians, dentists and pharmacists, however, cooperation from nurses should be sought.
(4) Under the current situation companies submit reports to the regulatory authority while reports from direct reporting are not transferred to companies. This should be improved to have mutual recognition of cases. All reporting should be centralized to the regulatory authority and its related organizations and comprehensive scheme which enables information exchange with WHO and signal detection as in Section 7 of Detailed Discussion should be reviewed. Actions including protection of privacy information could be necessary.

(5) The time frame of 6 months for EPPV is not considered long enough. The system and period of EPPV should be reviewed not only by requesting intensified reporting to companies but also by implementing measures to increase direct reporting.

To promote researches for signal detection and hypothesis strengthening / testing studies : from Section 7 of Detailed Discussion

(1) Regulatory authorities should recognize statistical significance of the signal detection, consider the introduction of signal index, and sponsor / support researches to utilize signal detection.
(2) Observational studies to strengthen / test hypothesis, especially case control studies should be developed. "Public organization" in Section 1 of Detailed Discussion should select and organize this type of safety studies as research project of non-company PMS.
(3) Signal detection and case control studies should be included in (3) and (4) of Section 4 of Detailed Discussion.

7. Ethical principles in PMS: Overview (9)

Ethical principles should be established in line with "Ethical guidelines for epidemiological studies": from Section 12 of Detailed Discussion

(1) Consent from individuals is required in case control studies with control arm of general population, however, individual consent is not necessary in spontaneous reporting, activities and research for safety surveillance such as signal detection, prospective cohort studies, and studies utilizing database.
(2) Ethical committee is necessary in principle, however, it should not be required for studies conducted with different drugs in similar system.
(3) It is requested to review "ethical guidelines for epidemiological studies" by taking 1 and 2 above into consideration. It is necessary to take similar consideration as excluding cancer in disease specific system or to add descriptions to keep consistency in the whole guideline.
(4) "PMS guideline" should be prepared in conformity with the ethical principles and scientific rules in Section 5 of Detailed Discussion.

Sections of Detailed Discussions

1. Issues on investigator initiated and public PMS

When a drug is started to be used in medical practice, it is appropriate to plan and implement PMS not only by the company which supplies the drug but also by health care medical professionals and regulatory authorities considering a study subject necessary in each party's point of view.

(1) Necessity and significance

In addition to the evidence for individual drugs collected by companies, results of studies clarifying characteristics in comparison among drugs in the same class or drugs of similar effects, and effects of concomitant use are requested in actual medical practice. PMS mainly conducted by investigators and public bodies is called as "PMS outside companies" in the following description.

(2) Required characteristics

Research subjects which should be conducted in PMS outside companies include:

a) Safety issues common to drugs in the same class or drugs of similar effects: Safety issues having social significance such as MHLW scientific studies evaluating causality between influenza encephalitis /encephalopathy and NSAIDs.

b) Subjects on efficacy common to drugs in the same class or drugs of similar effects: Efficacy issues not requiring evaluation of surrogate endpoint such as hypotensive effects but of true endpoint such as inhibition of development of cerebrovascular/cardiovascular accidents.

c) Subjects on concomitant pharmacotherapy or addition of pharmacotherapy to other therapy: Issues of studies evaluating development of new treatment or overseas standard therapies, such as studies on concomitant chemotherapies and adjuvant therapies.

d) Issues requiring evidence of off-label use

The studies which have public interest and may affect public health a), long-term large scale studies which are difficult for companies to conduct b), and studies in which multiple drugs from more than one companies are investigated c) are suitable as PMS outside companies, however, companies conduct studies for their own drugs d). d) is usually the issue of companies, but it is difficult for companies to conduct such studies when the issue considers orphan disease or pediatric use even if it is considered significant in medical practice.

(3) Relationship with companies

Investigators may receive drugs, drug related information, financial support, and sponsorship from companies, but operation of a study from its plan to its completion should be independent from companies and the operations should be fair and transparent. Publication should be actively sought, and conflict of interest with companies should be clearly specified. On the other hand, compensation is difficult when an accident occur in PMS of off-label use.

(4) Current issues

Many PMS studies have been conducted for drugs by company, however, PMS outside companies has not yet been carried out adequately. "Expert committee for clinical study guideline" and "Conference of large-scale clinical study network" have been started, but their systems are not yet available to determine, organize, support and implement appropriate PMS study subjects in timely manner. Insufficient funds due to inadequate financial support cannot be used appropriately and sufficient results have not been obtained. A number of long-term large scale clinical studies carried out in Western countries have provided basic information to guidelines such as treatment for hypertension as evidence of appropriate use, but there is less experience of such studies in Japan.

(5) Utilization of study outcome

It has been suggested as an issue by some medical investigators that even though valuable evidence is obtained in difficult situations, it is sometimes not utilized for appropriate use. Since companies have obligations to observe global safety studies, outcome of safety studies should be utilized for appropriate use regardless of type of the organisations which conduct the studies. Results of efficacy

study may be used within approved indication of a drug, but results on off-label use can be used only after a change in indication and dosage/administration is approved. When a company submits application using data of PMS outside the company, quality assurance of the data is necessary. It is discussed in Section 10 of Detailed Discussion concerning clinical trials. When a company does not submit application, it is difficult to utilize such data. Some measures are required for their utilization.

(6) Direction of improvement

PMS outside companies would not be developed until following improvements are initiated towards the current condition: investigators should recognize necessity of PMS and make efforts to conduct it, qualified personnel such as administrators, coordinators and researchers who plan and organize PMS should be developed, and environment to implement studies and financial foundation should be established.

(7) Recommendation: Measures to promote investigator initiated and public PMS

a) Financial support from public organizations, companies and other groups provided to PMS organizations having activities independent of companies and newly started individual research or research organization should be increased. It is also possible that support is to be given by pooling funds by contribution from companies according to their sales.
b) It is requested to establish mechanism to support and give financial assistance not only R&D but also PMS of drugs in the independent administrative institution to be established by integrating Pharmaceuticals and Medical Devices Evaluation Center (EC) and Organization for Pharmaceutical Safety and Research (OPSR).
c) It is requested to establish public organization with functions of selecting research subject of PMS outside companies, supporting organization and implementation of studies, and management of outsourcing, etc. and an organization which actually conducts studies should be included in the future. It is preferable to include such organization in the independent administrative institution in b) above when possible.
d) It is requested to establish Pharmacoepidemiology course to develop PMS investigators, coordinators and research managers at national health medical institute and one-year graduate school for development of workers to be newly founded.
e) It is recommended to establish a system of public studies premised on cooperation from companies, and a supporting system with public funds for issues such as orphan disease and pediatrics in which social interest is high and expansion of indication of drugs are desired.
f) It is requested to allow results of investigator initiated PMS to be utilized as re-examination application document and companies to provide transparent funds on the assumption that such PMS studies are independent of companies.
g) Methods to utilize evidence of off-label use to medical practice should be investigated, for example, revision of health insurance system.

2. Issues on companies

Almost all PMS studies have been carried out by companies in the past. In the future, PMS studies should share its roles with PMS outside companies according to their issues. However, responsibility to products ultimately lies with companies, and especially the responsibility to secure safety is significant.

(1) Issues in attitude of companies

In the past, some companies put emphasis only on development of products and negative attitude of just complying with regulations in post-marketing after obtains approval was seen. PMS has been considered less significant than product development. Number of patients in pre-marketing studies is few, it is obvious that conditions of pre-marketing studies such as targeted patients, method and period of administration, and concomitant drugs are different from those of post-marketing medical practice.

In order to establish appropriate use of drugs in medical practice, PMS should be planned and implemented with a view consistent from development to post-marketing, however, there were companies which did not have positive attitude to develop their drugs better through PMS.

While consistent planning from pre-marketing to post-marketing is required, appropriate measures for issues which occur post-marketing are also necessary. However, experience and knowledge of Pharmacoepidemiology are not adequate. Safety issues are increasing, and it is required to take rapid actions against unexpected issues, however, regulatory reporting and explanation to outside of companies may be delayed. Safety information should be highly transparent and scientific. Attitude of companies toward adequate explanation and appropriate measures for issues should be sought.

(2) Future direction

As for significant safety issues, it is desirable to cooperate with public entities as explained in Section 1 of Detailed Discussion. With regard to efficacy, issues on new indication which are difficult for companies or necessary for medical practice should be managed by cooperation with PMS outside of companies including investigator initiated studies to submit additional application as much as possible.

Personnel should be educated and developed by attaching importance to PMS and efforts should be made to expand organization by securing adequate people. It is not considered appropriate to abolish CEI with 3,000 cases as it is no longer a mandatory requirement. Making plans by returning to the fundamentals to seek methodology for research subject, adaptation of new methodology and effort to improve quality of PMS are also necessary.

(3) Recommendation: Position of companies in future

a) PMS should be adequately conducted with positive attitude of developing good drugs from pre-marketing to post-marketing and measures should be taken for issues timely. Negative attitude of just following the regulatory system should be abolished.

b) Safety information should be transparent and scientific. Safety issues should be managed promptly by achieving sufficient accountability for explanation.

c) Organization for PMS should be expanded by increasing awareness of importance and necessity of Pharmacoepidemiology, developing people and securing adequate personnel.

Qualification system for safety persons in companies by JSPE as one of the requirements for Manufacturing Marketing Supervisor-general or Safety Supervisor as described under the revised PAL.

d) If PMS outside companies advances as described in Section 1 of Detailed Discussion, companies should contribute to the funds to supporting groups according to their sales, supply drugs and information and provide transparent funds to studies independent of companies.

3. Issues on regulatory system and organizations

Japanese system started as ADR monitoring system in 1967 are complicated having been added new elements and revisions. While international harmonization of drug regulations are being achieved, the system including organizations to operate the regulations should now be reviewed.

(1) Systems in Japan and in foreign countries

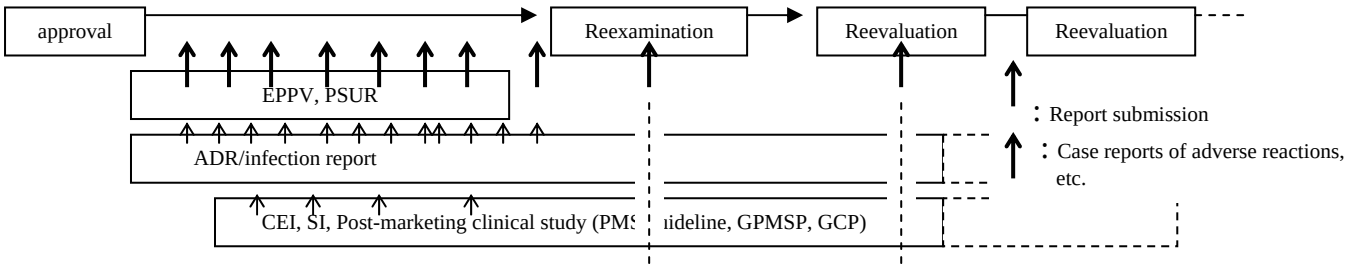
Western system has mainly been aimed at safety surveillance. The major source of the system in the US has been reports of adverse reactions from companies, however, reports from patients and consumers were added through MEDWatch and reports from pharmacists are increasing. In UK, adverse reaction reporting to CSM (Committee on Safety of Medicines) from physicians using yellow cards is the major source of the system. For the drugs marketed with a black triangle in the Data Sheet, all suspected adverse reactions are to be reported in the intensifying period of approximately 2 years after launch (after the period, unexpected/serious adverse reactions are to be reported.) In France, pharmacovigilance system is characterized by the process where adverse reaction reports from health care professionals collected in about 30 regional centers in the country are gathered to a national center for evaluation.

PMS system in Japan requires companies to conduct adverse reaction/infection reporting, early phase post-marketing vigilance, CEI, SI and post-marketing clinical studies and submit documents for early phase post-marketing vigilance, periodic safety reports, re-examination and re-evaluation.

(2) Issues on systems and organizations

Fig 1 shows outline of Japanese systems. Relationship of each system, studies and reports is so complicated that it is difficult to describe it accurately. For example, EPPV is explained as intensified evaluation and reporting of adverse reactions immediately after launch, but it has other aspects such as dissemination of information and calling attention to medical institutions. Although safety surveillance is important, repeated submission of reports for EPPV, PSR and re-examination would be burden to both companies and regulators. Idea to unify them to a single periodic report should be reviewed.

Fig 1: PMS reporting system between regulatory authority and companies



Centralization of ADR reporting to regulatory authorities in Fig 1 is also common in foreign countries. Direct reports from medical institutions are also centralized to regulatory authorities. WHO Uppsala Monitoring Center, UK MCA (Medicines Control Agency) and US FDA (Food and Drug Administration) have started to make signal detection (See Section 7 of Detailed Discussion) which uses collected data mandatory. Such operations related to safety surveillance should be conducted by regulatory authorities or their subsidiaries where data are centralized. FDA is conducting observational studies under contract with owners of database as explained in Section 9 of Detailed Discussion, and the UK database, GPRD, is managed by MCA.

Re-examination and re-evaluation are the systems which are not implemented in Western countries, but in some countries re-application is required for approval. Efficacy may be evaluated under re-application. As explained in Section 1 of Detailed Discussion, in long term large scale studies conducted by groups outside of companies, and in studies which evaluate efficacy of concomitant pharmacotherapies, the issue that evidence obtained as the study outcome may not be utilized as information on the appropriate use is due to the current systems.

While companies have conducted PMS with the methods specified in the guideline for re-examination and re-evaluation of the products, CEI and SI specified in the regulation are Japan specific terms and not globally valid. As explained in Section 5 of Detailed Discussion, study methods should be selected according to pharmacoepidemiological methodology, and it is not necessary for regulatory system to regulate methodology. It is useful for regulatory authorities and companies to discuss PMS plans and agree study methods, but methodology should be independent from regulations.

In terms of organization, it should be reviewed by considering Future PMS in Japan, since PMS is considered less important than review of NDA. Contact points of PMS are divided into two parts, Evaluation and Licensing Division for re-examination and re-evaluation which have nature of re-confirmation of approved items, and Safety Division for safety management such as ADR/infection reports and revision of "Precautions for Use". It may be a tactic to unify all operations related to PMS into a single organization. Since continuous management of safety information from development through marketing is also considered applicable, it is desirable to establish a system to reflect such data into draft package insert. Operations related to evaluation including re-evaluation and re-examination are outsourced to EC and OPSR, and there are inconsistencies between these organizations due to complicated operation system.

(3) Make use of data retained by authorities

Many data such as ADR, CEI, SI, Post Marketing CT, etc. are centralized and kept at authorities as figure 1 shows. Data that is useful as appropriate use information should be made into public and it is considered most of data are useful for PMS as later in Section 6 & 8 explained. PSR should be used to detect signals, while data of CEI/SI should be, after evaluation, sorted out and retained for the use in the next PMS since these data are seen as the result of observational studies and can be comparable.

(4) Recommendation: It is requested that regulations systems and organizations should be reviewed by considering following items.

a) Objectives and functions, international consistency and separation between methodology and systems should be considered.

b) Consistency of organization and operational purposes, and simplification of organization should be considered.

c) It is requested to develop experts having neutral position who can conduct PMS permanently and to establish organization specialized for PMS. It is preferable to include pharmacovigilance study organization in future.

d) It is requested to make database of the data of spontaneous reports of ADR, PSR, CEI and SI accumulated in regulatory authorities, and to make them available for use by companies, research institutes, etc., under certain condition.

4. Issues to increase interests of medical professionals in PMS

Interests in PMS could not be increased only by emphasizing the significance of PMS to health care professionals. Back ground issues are not limited to PMS, but there are issues of researches and educations common to all clinical studies. Historical consideration about actions toward improvement and making efforts in long range will bring develop of PMS.

(1) Background issues

Based on the idea that treatment cannot be initiated without diagnosis, therapeutics have been considered less significant than diagnostics in clinical medicine. Basic researches have been traditionally considered significant and clinical studies with patients less significant. In pharmacological field, studies on pharmacotherapies have been considered less significant than basic researches, and there have been issues that pharmacists have insufficient knowledge and experience on pharmacotherapies. Researches on pharmacotherapies have double handicap: therapeutics against diagnostics and clinical researches against basic researches. PMS was less interested especially compared with pre-marketing research. These issues have affected education and medical students have not been able to spend much time for therapeutics, because they are busy in understanding symptoms, pathology and diagnosis. Pharmacotherapeutic education has also been insufficient to pharmacological students.

(2) Current status

EBM has been emphasized in recent years, and significance of clinical studies with patients has been recognized. Concerning pharmacotherapies, opportunities may increase for health care professionals to voluntarily conduct or participate in researches to seek evidence, and to critically examine studies conducted by others. In 2002, PAL revision made reporting of diseases/deaths of possible ADRs from medical professionals mandatory. In 2004, two-year post-graduate training will become mandatory for clinicians. These current changes may enhance increase of health care professionals who have interests in pharmacotherapy, and also intensify development of personnel who want to be a pharmacotherapy researcher. Such trends may enhance interests in PMS and it will make PMS advanced.

Since pharmaceutical medicine is being established, and interest of hospital pharmacists is increasing, roles of pharmacists in medical practice will become more important according to progress of separation of dispensing/prescription, and education period of qualification for national examination for pharmacists is to be extended to six years.

(3) Recommendation: Request to increase interest to PMS and to educate qualified persons who will achieve improvement of pharmacotherapies

a) Not only pharmacological actions of drugs to organs but also PMS which is conducted to establish appropriate use during development phase and post-marketing phase of drugs should be emphasized in the undergraduate education of medical students.
b) National examination for medical practitioners includes only about 30 questions on pharmacotherapies. In most of the questions, selection of an appropriate drug is asked according to its pharmacological actions. It is recommended to increase questions requiring overview of pharmacotherapies, including efficacy and safety.
c) Post-graduate training of medical doctors should include practical experiences such as methodology of intervention studies and observation studies, EBM, development course of drugs, evaluation methods of efficacy and safety in development and post-marketing phases as well as clinical pharmacology, clinical epidemiology and pharmacoepidemiology.
e) Concerning education for pharmacy students, concepts of the model course defined by the Pharmaceutical Society of Japan in view of increase of the years for education of pharmacy students to six from four should be realized, and the professional course should include pharmacotherapies, methods of clinical studies, and PMS systems.

5. Practical use of pharmacoepidemiology

In PMS, observational studies and clinical trials (intervention studies) should be properly utilized in accordance with pharmacoepidemiological methodology. Scientific principles common to all PMS investigations will be discussed below. Although research objectives vary, when they are classified as 1-11 below, methods/designs corresponding to research objectives are summarized as Fig 2.

Fig 2: PMS research objectives and corresponding study method

Research objectives	1. Detection of unexpected serious AE/ADR cases	2. Generation of hypothesis concerning causal relationship	3. Hypothesis strengthening/testing concerning causal relationship	4. AE/ADR profile - frequencies and sequential change	5. Efficacy/usefulness in medical practice (QOL, etc)	6. Long term prognosis	7. Discovery of new efficacy	8. Hypothesis strengthening/testing concerning efficacy	9. Efficacy and safety in patients with special backgrounds	10. Concomitant therapy - efficacy and safety including interaction	11. Understanding of use of drugs in actual practice and evaluation of appropriateness	
Method and design												
Spontaneous reporting	⊙											○: method which should be selected ⊙: method considered as the first choice
Case series	○	⊙		○			⊙					
Signal detection		⊙										
Analysis of secular trend		○	○	⊙								
Drug utilization study					○		○		○		⊙	
Case control study			⊙					○		○		
Cohort study			⊙	⊙	⊙	⊙	○	○	⊙	⊙	○	
Clinical trial			○			⊙		⊙	○	⊙		
Meta-analysis			○			○	○	○		○		

(1) Objective and method of safety study

Serious and less frequent adverse reactions are often unknown, when drugs are launched. Detection of such ADRs is important objective of PMS. It starts after such cases are detected in 1. While spontaneous reporting is not a study method, it is included in above list, because data of AE reports regardless of causality are essential for objective 1.

When cases are accumulated, causal relationship with the drug used would be suspected. 2. Generation of hypothesis concerning causal relationship implies it, and when it is proceeded to statistical hypothesis strengthening and testing, unknown ADRs could be detected. The objectives 1-3 are continuous, and the following method which belongs to descriptive study is used for generation and strengthening of hypothesis:

Case series is the study method to indicate cases in specific area or medical institutions in a table of case chart. Studies on statistic method have been started globally to search relationship between an AE and a drug by using case series and accumulated data of spontaneous reports concurrently. In Fig 2, it is described as “signal detection”. Analysis of secular trend is a method to examine correlation by collecting frequency of an AE and manufacturing volume/patient exposure of a drug. The study is year-to-year secular trend, if annual data are used as unit, and ecologic study, if local population is

used as unit. The method does not require data of individual case, but can use populational data. Analysis of year-to-year secular trend is applicable to the research objective 4., sequential change of AEs/ADRs.

Method of analytic study, which is one of observational studies, can be applied to estimate causal relationship between a drug and an AE statistically and to quantify risks as below.

Cohort study is a method to investigate the occurrence of AE by following up a group of users of the drug and a group of non-users of the drug in medical practice. There are prospective studies in which investigations are toward the future from the beginning of the study, and retrospective studies in which groups are made according to the past medical records and the data are examined sequentially towards the present. Control of no-treatment group is placed to evaluate effects of drug use. Several groups are made according to drugs and dosages in consideration of the study objective, or control group of standard drugs or low dose groups instead of non-treatment group can be applied.

Case control study is a method to analyze relationship between AE and drug by investigating and comparing drug use and other risk factors between risk factors between a case group of patients who experienced the AE and control group of patients who did not. It is always conducted retrospectively. Cross sectional study investigates factors such as drugs and outcomes simultaneously, and it is distinguished from longitudinal study which cohort study conducted along lapse of time, and case control study conducted retrospectively.

While in observational study, external validity which can grasp the population without bias is important, treatment/non-treatment groups and case/control groups may have bias such as age and risk factors including concurrent disease, and results may be distorted. On the other hands, an intervention study in which subjects are allocated randomly is controlled not to cause bias between groups. It has internal validity, but sometimes lacks external validity. It cannot be determined which one is superior: observational study or intervention study. The method should be used after characteristics of each study are fully understand and the results should be interpreted accordingly. In order to improve the quality of observational study, it is required to secure external validity, organize groups by selecting subjects from population to avoid biases among groups, collect accurate data on cause and result by through follow-up on drug use and occurrence of AE, and utilize analysis method to adjust effects from bias. Because it runs a risk to make conclusions with a single study, analysis should be conducted carefully. Quality of the intervention study is to be discussed in Section 10 of Detailed Discussion.

(2) Objective and method of efficacy studies

Possible on efficacy objectives are 5, 6, 7 & 8 in Fig 2. Evaluations such as QOL are done not only by changes in symptom but also by outcome in 5 and long-term prognosis in 6. Detection of unexpected ADRs as well as 7 and 8 concerning unknown efficacy are also objectives of the studies. Case series may induce detection of new efficacy.

In safety study section, cohort study was explained as investigation of occurrence of AE, however, result of therapy and final results such as cure and QOL may be investigated instead of AEs such as occurrence of concurrent disease or death, and thus cohort study is also widely applicable to efficacy objectives. Even in the studies with parameters of AEs such as occurrence of concurrent disease and death, detection of increase trend of them due to the drug is a safety study, but a study to expect decreased trend is an efficacy study. Not only cohort study but also case control study are applicable for studies with objective of efficacy.

Concerning objective 8 to test hypothesis developed in observational study, clinical trial with intervention, especially randomized controlled trial (RTC), is the first choice. In “6. Long-term prognosis study”, decrease of rare diseases such as cerebro/cardio-vascular diseases (efficacy), or increase (safety) is evaluated. Therefore, parameter of evaluation is true endpoint but not surrogate

endpoint. In a safety study in which intervention should be avoided, the observational study should be selected and measures should be taken according to its result.

(3) Other research objectives and methods
Other objectives include 9 for patients with special background such as pediatrics, elderly and concurrent disease, 10 for patients using concomitant drugs, and 11 for information of drug use. Observation study or RCT may be selected for 9 and 10.

Target of PMS is to add evidence to objectives in 1 to 10 and to take measures when there is a issue concerning appropriate use.
As for the objective to understand the drug use in actual practice (11), drug utilization (DU) study is necessary. Researches to investigate information on subjects such as age, disease, concurrent condition, drugs in use, dosage, dosing period according to drug class or by product are classified as drug utilization (DU), researches to evaluate appropriateness by making comparison to the appropriate use condition obtained from 1 – 10 are called drug utilization review/evaluation (DUR or DUE). The methodology for DU corresponds to cross sectional study.

Evaluation of appropriateness links to package insert in terms of individual product and to revision of therapeutic guidelines in terms of target disease or drug class. It is possible that a severe issue may link to product lifecycle. Comprehensive evaluation of risk and benefit is necessary, and comparison with similar drugs is required. Therefore all results of PMS should be disclosed to the public. Results from multiple researches would not always coincide and meta-analysis is used to intensify evidence by evaluating multiple researches comprehensively.

(4) Current situation and issue of PMS in terms of methodology
PMS should be conducted under pharmacoepidemiological methodology, however, CEI, SI and post-marketing study by companies are classification by the regulatory system and only a few considerations have been given to methodology.
Although CEI and SI correspond to cohort study, principles of observational study and characteristics of clinical trials in PMS are not understood enough and case control studies which are indispensable to safety research have not been conducted as expected.
These issues and measures for improvement are discussed at each discussion section. Fig 2 comprehensively summarize post-marketing research objectives and methodologies to be selected for corresponding objectives.
Regulatory system is necessary, however, companies are expected to conduct PMS because of objectives, not due to regulatory system.

As discussed in Section 1 of Detailed Discussion, groups outside of companies should conduct PMS for the issue difficult for companies to conduct. Although the current PMS guidelines are guidance from regulatory authority, scientific guidelines which would be applicable to all PMS is required to improve the current situation.

(5) Proposal: To utilize Pharmacoepidemiological methodology in PMS
By combining scientific principles in Fig.2 and ethical principle in Section 12 of Detailed Discussion, “PMS Guidelines” which are applicable to both PMS by companies and PMS outside of companies should be prepared in cooperation with relevant parties.
It may be difficult to apply Fig.2 to actual issues, however, efforts are necessary in the Guidelines to approach to the ideal principle without compromising with the current situation..

6. Issues on spontaneous reporting

A case report from an individual physician was the start of the thalidomide issue, and safety surveillance system with spontaneous reporting was established. Safety surveillance is the starting point of PMS. Collection and evaluation of spontaneous reports, as well as countermeasures are significant. In Japan, reporting numbers are not many and issues of spontaneous reporting is discussed in this section.

Reports include spontaneous reporting from physicians and pharmacists, and solicited reporting related to studies and investigations. All of such reports are defined here as "spontaneous reports", and among them, reports from medical institutions to companies are called company report and reports from medical institutions directly to regulatory authorities are called direct reports.

(1) Necessity, significance and limitation

ADRs of incidence less than 1/1000 include serious ones, and such ADRs cannot be detected before launch in many occasions. Spontaneous reports are essential not to overlook unexpected ADRs of lower incidence. If detection of a serious ADR delayed, it may cause social issue due to loss of many lives affecting the product's life cycle. Safety surveillance with spontaneous reports is, therefore, the most significant objective of PMS. Spontaneous reports are also necessary to understand situation of occurrence and change of expected ADRs. The issues to detect unexpected ADRs are discussed below.

It is difficult to identify causal relationship with a drug used to a patient in individual cases unless rechallenge test is conducted. Many cases require statistic inference from observational studies. Limitation of spontaneous reports is that individual case reports only indicates "suspected ADR". In urgent safety issue, it is required to evaluate causality in individual cases. In observational study, however, analysis of causal relationship is required based on reports on AE, as in Section 7 of Detailed Discussion.

Even if spontaneous reports are accumulated, it is impossible to determine incidence of ADR/AE, when extent of patient exposure is not available. It requires cohort study explained in Section 8 of Detailed Discussion. However, if patient exposure can be calculated according to production/delivery amount, estimation according to descriptive epidemiology is possible (please see Section 5 of Detailed Discussion).

(2) Current issues and actions toward improvement

Changes in number of reports in Japan and the result of comparison between Japan and US/UK/France using number of reports per 1 million population were described in Appendix (not shown).

Increase of reporting numbers since 1995 was probably due to implementation of GPMSP, revision of safety information reporting system, and so on. The number is leveling off recently. Simple comparison of data among each country is difficult due to differences in regulations. Though the data of 1995 are rather old, it seems that reporting number is fewer in Japan than other countries.

Underreporting is a global issue. Its factors include legal issues which is difficult to be solved, but the number will not increase unless health care professionals are aware of the issue discussed in Section 4 of Detailed Discussion. Health care professionals may raise questions as to what should be reported. It is important to seek their understandings by explaining them in activities to promote their knowledge. Cases should be reported if they are possibly caused by a drug, serious, "I have never seen", unusual, etc. It is one technique to shown medical institutions which report many AE/ADR cases as the collaborative institutions of appropriate use of drugs.

Determination of causal relationship requires data understandable to the third parties who conduct evaluation in terms of patient information, sequential change of the event, diagnosis and temporal relationship with drugs including concomitant drugs. Not only number of reports but also their high quality are required. It may take time to follow up and actions may delay. For both company reports

and direct reports, case report form should be standardized, and it is preferable to add special items for key ADRs specific to a product.

Follow-ups and evaluation require expertise. Workload increases with increase of reporting numbers. System to intensify resources on important issues is necessary. Grading of significance is determined by factors such as expectedness and seriousness of the AE/ADR. Standard[5)] of follow-up investigation posed by CIOMS V is considered effective for efficiency.

Causal relationship becomes an issue when cases are accumulated. Judgment should be made by using all the accumulated reports. In the future, mutual alignment system with data from company reports, direct reports and overseas reports collected in WHO is ideal. Study to approach to the ideal situation has been started in the world.

When the data can be linked with other data such as medical records, death registration and prescription data, serious ADRs of lower incidence are considered detectable. It is the method which can be available after database is fully equipped. This topic will be discussed at Section 9 of Detailed Discussion. Spontaneous reports of AE/ADRs of considerably lower incidence should be continued as far as possible. Future safety vigilance model would be the combined methods indicated in Appendix(not shown).

(3) Recommendation: It is proposed to intensify spontaneous reports as described below to meet increasing safety issues

a) After PAL revision in 2002, it should be known to related persons without exception that spontaneous reports became obligation for health care professionals (Article 77-4-2 Item 2 of PAL). This should be informed to promote their awareness to understand the revision thoroughly.
b) Forms of the direct report from health care professionals and company report should be standardized and simplified. Reporting items and methods should be well educated to health care professionals and company personnel, and it should be stressed that reports of serious cases and unexpected ADR cases are specially important.
c) While the reporters of direct reports are specified as physicians, dentists and pharmacists, it should be examined[6)] to request assistance from nurses.
d) Company reports are submitted to regulatory authorities, but direct reports are not transferred to companies. Such practice should be revised and mutual cooperation should be examined. Regulatory authorities and its related organizations where all reports are collected should play as a leading roles in future plans to establish general systems including information exchange with WHO and signal detection described in Section 7 of Detailed Discussion. However, measures to protect privacy should be necessary.
e) Six months of EPPV period is considered not long enough. Intensification of reports should not be required only to companies, but measures should be taken to increase direct report in consideration of a) above to review the details and period of this requirement.

7. Issues on signal detection and case control study (Signal detection and strengthening / testing of hypothesis)

When case reports of a serious possible ADR are continuously collected, and many of them have temporal relationship with the use of a drug, and other factors are considered unlikely, causal relationship with the drug is suspected. Regulatory actions such as Dear Dr Letters have been taken after accumulation of individual case evaluation, however, researches are being globally conducted[4)] for signal detection which can statistically find out significant (possible) ADRs to be reviewed with priority.

WHO Uppsala Monitoring Center (UMC) defines the signal as "information concerning possibility of causal relationship between an AE and a drug which was not identified or imperfectly confirmed".

(1) Necessity and significance

As it is historically shown in incidents such as the thalidomide issue, careful observation of individual physician may become signal detection. Organized efforts of hospitals, companies and regulatory authorities are essential for safety surveillance. In the future, a method of statistic signal detection, which is called data mining, will become a significant procedure.

A signal is hypothetical information indicating that the event may be possibly related to the drug, though, actually, there may be no causal relationship between the event and the drug. Hypothesis strengthening/testing studies are required following to signal detection. Observational studies to identify high risk subjects and to quantitate risk are important to establish appropriate use of drugs. Case control study is effective, especially when suspected ADRs are few.

(2) Current situation and issues

In Japan, method of signal detection is not yet well developed, and hypothesis testing by observational studies where case control studies are taking major part are scarcely conducted. In Western countries, statistical methods were tried to be applied to signal detection by using large data from accumulated spontaneous reports in 1990s. Signal parameters such as PRR (proportional reporting ratio) by MCA, UK., and RR (signal score) by FDA, and IC (information component) by UMC have been put into practical use. Signal parameters, which indicate whether causal relationship should be considered or not, are now becoming indices common to regulatory authorities and companies. On the other hand, there are no activities in Japan at this moment to utilize the signal parameters of this kind.

UMC is providing signal parameters of specific ADRs of specific drugs to companies as pay service. In the US, there are companies which provides additional information signal index from the data obtained from FDA. In Japan, Japan Drug Safety Research Unit will start a business to provide a brochure to summarize the result of the above mentioned method applied to spontaneous report data published on Website by OPSR.

In Western countries, case control studies are carried out after signal detection concerning such issues as Ryere's syndrome. Many observational studies have been carried out as shown in appendix to Section 9 of Detailed Discussion(not shown). Only a few studies are carried out in Japan except for the study of relationship between development of haemorrhagic gastrointestinal ulcer and NSAIDs[7)] conducted by Asaki et al[7)]. Case control studies are often conducted as investigator initiated studies in the West. It is recommended to improve environment to conduct studies as indicated in Section 1 and 4 of Detailed Discussion and to enhance interests of health care providers in safety surveillance.

Many safety studies are carried out using database in the West. There are opinions indicating that case control studies cannot be conducted in Japan since databases are not provided. As discussed in Section 9 of Detailed Discussion, databases are not perfect even in the West and they are always used with compensation for their defects. Recently, studies have been started by utilization of electronic data of hospitals, such as a study concerning ACE inhibitors and senile pneumonia conducted by Okaishi et al[8)], a study concerning Ca antagonists and myocardial infarction by Ohyama et al[9)]. Such studies are expected to increase in future. It is difficult to conduct such studies smoothly without

cooperation among departments of hospitals for hospital based studies and without cooperation from community for community based studies. Not only medical but also social and national consensus is necessary to conduct such studies.

(3) Future direction

Observational studies concerning safety have not always had specific reasons of "Why should such issues be discussed?". When statistical methods are made practical for signal detection, way to hypothesis strengthening/testing studies and studies to quantitate risk could be clarified, and plan would be appropriate. In the communication among regulatory authorities, companies and researchers, if signal parameters are used commonly, safety surveillance system could be developed to a system different from current one, its transparencies could be increased, and it could respond to social needs sufficiently. The contents, scope, methodology, etc. of information disclosure will be considered in the following sections of Detailed Discussions.

(4) Recommendation: Following items are requested to intensify safety surveillance along with the recommendations a-e in Section 6 of Detailed Discussion

1. Regulatory authorities should recognize significance of statistical signal detection, and conduct research for practical use of the parameters or support/promote such research.
2. Observational studies to strengthen/test hypothesis, especially case control studies should be developed. These kinds of safety studies should be included in (3) of Section 1of Detailed Discussion (public organizations select and organize tasks of PMS outside of companies.)
3. Signal detection and case control studies should be included in (3) and (4) of Section 4 of Detailed Discussion (education and postgraduate training).

8. Issues on cohort study

CEI is regarded as follow-up investigation implemented to avoid intentional case selection in actual use of the drug. It is regarded as a cohort study although there is no control group. Similar investigation in special subjects is SI (special investigation) , and this is also a cohort study. Though such recognition may not be common, a cohort study is a significant method to strengthen and test hypothesis, and it should be conducted scientifically and to fulfill its objectives.

(1) Necessity

Because progress of clinical studies in Japan is slower than the West in spite of various measures of promotion and improvement, number of Japanese subjects could be less when international development is adopted, and development of products using bridging overseas data is increasing. It may be necessary to add patients after launch, and there may be a challenge in cohort study to confirm that the result of clinical trials in overseas is applicable to a domestic population with the same backgrounds. Therefore, companies should conduct cohort studies as PMS, after consistent plan is established throughout before and after launch.

In clinical trials of development phase, infants, elderly patients and patients with special backgrounds such as concurrent disease are often excluded from the studies, and efficacy and safety information of concomitant therapies is not sufficient. Well planned cohort studies are effective to collect such information. Because it is significant task of not only companies but also health care professionals to understand actual use of drugs in early phase of post-marketing, and to link the issue obtained in such period with the information on appropriate use, cohort studies should be carried out in the manner appropriate to the research objectives.

Spontaneous reports should be extended and intensified to detect serious unexpected ADRs. It is necessary to understand number of subjects who are given the drug to find incidence of ADR/AEs including expected ones by using cohort studies.

(2) Current issues

When SAMM Guideline (Guidelines for company-sponsored safety assessment of marketed medicines) was being prepared in UK, several issues were discussed on cohort studies which follow up registered drug users. Background of this discussion may include confusion with clinical trials without control group, and inadequate understanding of characteristics, objectives and methods of observational studies. It includes following issues, which may be applicable to Japanese situation.

- Studies including control groups are few, but comparison is essential to test causal relationship between an AE and a drug. Comparison is desirable in studies to understand incidence of usual ADR/AEs. Comparison of profile of incidence showing what ADR/AEs are frequent/rare in which drug, will become review material of causal relationship, and also useful as information on the appropriate use to select pharmacotherapy.
- A drug prescribing for research purpose is intervention to treatment. As studies under actual practice, intervention should be avoided by registering patients after prescription without exception, and inclusion/exclusion criteria should not be established. The patients are excluded only when administration of the drug is contraindicated to them. Although sequential registration in CEI is a thoughtful method to avoid selection bias, actual condition should be examined whether the registration is being carried out as planned, and whether bias could be avoided when the registration is carried out appropriately.
- Results of cohort studies conducted by companies are scarcely published. Even if they are published, the publication is late. There are no occasions to be criticized from relevant groups, even if the results are actively published on medical journals, therefore, improvement of the study method does not progress. Cleaning case report forms of CEI and SI and preparation of re-examination require enormous amount of time and resources. The issues that too much informations are included and the meaning of the investigations are ambiguous, may cause the fact that results are not published. It is time to review how PMS should be established by considering the fundamentals of method for objectives.

(3) Actions toward improvement

Obligation for companies to conduct 3,000 cases of CEI was abolished, but necessity of appropriate cohort studies still exists. Companies have to conduct studies not in compliance with regulations but by selecting methods of cohort studies according to the objective. At present, most of such studies will be carried out by companies, however, such studies could be conducted by groups outside of company and caution for the current issues discussed above should be necessary for studies conducted by outside of company as well as by companies.

Concerning issues of intervention and selection bias, retrospective study is one of the measures to be taken (Section 5 of Detailed Discussion). To make such studies feasible, it is expected that database discussed in Section 9 of Detailed Discussion is established as soon as possible. In prospective studies, it should be mandatory to select subjects after prescription, and methods of PEM (Prescription-Event-Monitoring) should be referred.

Although publication and disclosure of results is not issue only for cohort studies, results can be referred to appropriate use of drugs if data are accumulated in each area and can be accessed by anyone. CEI data on more than 800 drugs and more than 7,000,000 patients have been already accumulated in regulatory authority. According to a study conducted by RAD-AR council in which CEI data of several antihypertensive drugs were accumulated, useful information for appropriate use could be obtained. In the future, it should be confirmed whether similar methods is applicable to drugs of other classes, and data should be accumulated in database which can be used at any time after re-examination is finished.

When publication/disclosure become mandatory, quality of the study becomes concern and it then will be improved. Standardization of each area will be proceeded. When study results are published, the data can be used as "historical control" of future studies, and it is useful for studies without control groups.

(4) Recommendation: to make cohort study as potent method of PMS

CEI and SI are regulatory terminology which are not applicable internationally. As in Section 5 of Detailed Discussion, the terminology for the methodology should be used and it is recommended to use as "cohort study". Cohort study should be used as potent method of PMS as follows.

1. Guideline should include that intervention and selective bias should be avoided in cohort studies, and that control group should be put in the study if possible.
2. When a company plan a study in which the control group consists of users of other drugs in actual practice , mechanism to avoid bias should be established including consignment to a third party.

9. Issues on establishment of database

PMS observational studies can be conducted retrospectively with utilization of already accumulated medical records. In the West, many studies are carried out by using database established in local area or hospitals.

(1) Necessity and availability

Prospective studies require period to follow up subjects and to collect data, but subject follow-up is not necessary in retrospective studies using accumulated data. Period of retrospective studies can be shortened, if medical records are input into study database, and the data such as disease names are accurate and good quality with efficient data collection. It is specially effective, when a safety study requires its result promptly.

Observational studies without intervention can be conducted, if database sufficiently reflects actual drug use, and data is extracted carefully. Observational studies of high accuracy and quality on both efficacy and safety are possible by a large scale study involving many patients and community people, and such studies are specially effective for case control study of rare serious AE cases.

(2) Issues in the past and at present

From 1993 to 1996, MHW scientific research concerning database was conducted, but it did not lead to establishment of a database unfortunately. The time was not right for such initiative because experience of observational studies was lacking and necessity of the database was not recognized widely at that time. However, observational studies have gradually increased and it seems that the opportunity is coming.

Concerning the use of hospital information system, case control studies have been carried out by Okaishi et al[8] for ACE inhibitors and senile pneumonia, and by Ohyama et al[9] for Ca antagonist and myocardial infarction. Workshop committee of our society conducted a drug utilization study[14] of antihypertensive and antibacterial agents. However, all of the studies are carried out in a single medical institution with small scale and number of subjects in case control studies is small. In addition, arrangement of data in communities has not yet advanced.

(3) Factors hindering arrangement of database

In the West, regional and hospital medical data are input into databases in cooperation with public medical assurance (Medicaid), Health maintenance organization (HMO) and general practitioners, and such databases contribute to PMS. However, there are some defects and difficulties relating to creation in these databases, and there is no ideal database yet. Problems occurred during or after creating such database are listed below. The situation is same in Japan. Databases should be created after overcoming difficulty, maintained and used with understanding and compensating their defects.

- Cooperation of multiple hospitals is desirable in hospital information system. Standardization of data contents and their maintenance in each hospital is necessary in the first place. Standardization of data and standardization after data-integration are difficult when data are integrated among multiple hospitals and general practitioners, however, it will serve more practical use once integrated.
- When original systems are intended to improve daily routine work concerning payment and handling of health insurance, etc are integrated for research purpose, there are many issues which should be overcome to integrate data for research purpose, such as data format and barrier between administration bodies.
- When medical and pharmacy data are integrated, age, sex and physician's name are used as key items to make record linkage, but complete linkage is difficult when private information is protected.
- When integration of different information systems is necessary, more advanced breakthrough of IT technology is required than that in single system.
- There is more or less bias between registered members of database and whole population.

- All data such as disease name of health insurance are not always correct, and it may be necessary to confirm the data and supplement them for implementation of appropriate studies by examining the initial data such as patients' medical records, etc.
- Hospital data include serious event data, but they often do not include symptoms in many cases.
- Because people may take the health insurance and may withdraw from it for their reasons, constituting members of a database may change. Some of them cannot be followed up. It may be necessary to make efforts to establish linkage to national/regional death/disease registration.

These problems can hinder creation of database, but related organizations must commonly recognize significance of database creation, cooperate each other and make efforts to solve above problems. Improvement of defects is eternal issue. GPRD was established as VAMP in 1987, and experienced several large-scale revision, and is existing as current GPRD. MCA maintains and improves GPRD. Companies can use it under certain conditions, if it is used for research purpose. It is available to foreign companies.

(4) Future direction

Hospital information systems are rapidly advanced in Japan. Integration of multiple hospital systems is considered to be the earliest way of developing a database. Concerning regional data, electronic medical record transfer is being attempted between large hospitals and regional clinics such as International Medical Centre and Shinjuku-ku, Chiba prefectural Togane Hospital and Yamatake-area, Kumamoto University and Kumamoto City in cooperation with Medical Information System Development Centre. Development of regional database and use of such data for PMS are expected. Medical fee bill receipts including broader drug use are important PMS data source. System should be established within several years to advance computerization and to describe accurate disease names related to comprehensive medical care, as well as to complete database for PMS.

(5) Recommendation: Towards establishment of database

It is recommended to incorporate data of medical practice into database to utilize it for observation studies of PMS.

1. Some leading body should be established in regulatory authorities or their related organization to establish database by building a system with financial support and with cooperation from regulatory authorities, medical institutions, health insurance societies, academic societies and companies.
2. Maintenance and improvement of database should be conducted by a neutral, non-profitable organization and by public funds. The organization should be managed to accept access from outside organization such as companies under a certain condition.

10. Issues on clinical trials

Clinical trials have the leading role in new drug development. In PMS, randomized clinical trial (RCT) may be used as an efficacy study. RCT is mainly focused in this section, however, its nature in PMS is different from that in development phase.

(1) Necessity and importance

Efficacy in long term use of a drug and concomitant use with other drugs are not yet confirmed in many occasions before marketing. RCT in PMS is necessary for statistical testing of hypothesis concerning efficacy. Results are important as reference for appropriate use of drugs.

(2) Epidemiological nature

Comparability between groups to be compared and internal validity in RCT are satisfied with random allocation. In PMS, generalizability that the results of statistical test are applicable to common medical practice, i.e. external validity (See Section 5 of Detailed Discussion) should be considered. Therefore, subjects well representing source population such as hospital or region should be selected.

(3) Characteristics as long term large scale study

For example, in a study of an anti-hypertensive drug to test preventive effect on cardiovascular complications, the primary endpoint is changed to "true endpoint" of occurrence of complications after launch from "surrogate endpoint" of anti-hypertensive effects used in the study before approval. Therefore, in many cases, RCT in PMS requires much longer follow-up period than before approval. When decrease of AEs including complications is expected, the study may become a prevention study, but in many studies, many patients are required due to low incidence, then it has characteristics of long term large scale study. For example, in US ALLHAT[15)] study, 33, 357 patients were followed up for a mean of 4.9 years, and in WHI[16)] study, 16,608 women were followed up for a mean of 5.2 years.

In most RCTs before approval, reference drug is limited to one drug. In medical practice, many drugs were compared relatively, or comparison of combination therapies is sought in studies of prevention/treatment of cancers and life-style related diseases, etc. Therefore, it is difficult to conduct such studies by one company. Number of group and patient number may increase if treatment arms include non-treatment and/or placebo. Thus the study could become large-scale.

Long term and large-scale studies should be planned as simple as possible having "simple large" characteristics are desirable. It is important to realize generalizability and feasibility. All RCTs of PMS are not long term large-scaled studies, and RCTs similar to those before approval such as studies to add new indication conducted by companies are also conducted in PMS, but attention to generalizability should be necessary.

(4) Relationship with safety evaluation

Observational studies are considered as the first choice for safety studies, especially for studies of serious AEs, however, differential use with RCT should be agreed by experience retention. Efficacy studies of the primary or the secondary prevention expecting decrease of AEs are possibly conducted with RCTs, but hypotheses expecting decrease of AEs are not always reliable, and it is difficult to determine study method. Interim analysis should be carried out in consideration of possible unexpected outcome, and examination is necessary for continuation of the study or change of the study plan in view of the interim analysis result.

In long term large scale studies, primary results on efficacy are most interested, but safety data as well as primary endpoints should be carefully examined. Although efficacy endpoints may be different among studies, safety data could be generalized and evaluation of AE grading should be standardized to make comparison with other studies or to make comprehensive evaluation possible.

(5) Quality of the studies and data

Quality of long term large scale studies is evaluated according to elements such as whether the objective was appropriate as PMS, whether the study has generalizability and comparability, whether

the study was planned according to the principle of “simple large”, and whether the study was conducted according to the plan and analyzed according to the principle of ITT (intent-to-treat).

In a study for a new indication conducted by a company, quality of data is assured by quality assurance system which is standardized in conformity with GCP, and quality control activities in operation. Inspection of the data is carried out at the study sites. Such standard does not actually exist in studies outside of companies, but even if a study is not related to NDA approval, the study should be conducted with the procedures and written documents controlling plan/implementation of the study and data collection/analysis. The study coordinators are necessary at study sites, but qualified persons for this role are insufficient.

While long term large scale studies should also be conducted in conformity with GCP, detailed procedures specified in GCP is not appropriate for the principle of “simple large”. Quality assurance method considering balance with cost is necessary.

(6) Current situation in Japan and actions toward improvement

Long term large scale studies have just started in Japan, and experience of such studies is scarce. However, public organizations and the third party organizations such as NIH and SWOG in the US, and MRC in UK are operating such studies including management of plan and implementation, and analysis/evaluation and publication of their results. Evidence of long term prognosis is essential for improvement of public health, and development of clinical studies in PMS in Japan is necessary for evaluation of drug efficacy in prevention of cerebro/cardio-vascular diseases and life-style related diseases and for cancer treatment in Japanese population.

(7) Recommendation: It is recommended to take following measures in addition to 1-4 proposed in Section 1 of Detailed Discussion in order to develop clinical trials required in PMS

1. A role of clinical study coordinator who is in charge of management of a study and quality assurance of data should be established, and fulfillment of education and training to develop qualified persons, and assignment of such persons to medical institutions and accumulation of their experience in medical institutions should be sought.
2. In a long term large-scale study, idea of “simple and large” should be applied in plan, implementation, management and analysis. Especially for quality assurance of data and inspection, caution should be given to balance between its implementation and cost, and it is preferable to standardize the procedure with emphases on essential data related to primary endpoint, significant baseline parameters and SAEs.

11. Issues on meta-analysis

Each clinical study may have insufficient statistic accuracy and power, so that results may vary among studies. In such condition, definitive result may not be available by individual studies. Meta-analysis is an analysis method to integrate existing study results to compile conclusions in such situation. When the method is used appropriately, it can be effective to confirm evidence of efficacy and safety in PMS with the objective of appropriate use of the drug.

(1) Current situation

Meta-analysis is utilized for medical technology assessment in view of public health, and for decision making in diagnosis and treatment of individual patients in clinical epidemiology. The concept of choosing pharmacotherapy to a patient based on appropriate evidence is clinical epidemiology, and it is recently called EBM. This is linked to appropriate use. Meta-analysis has been mainly applied to RCT to evaluate efficacy, however, it is also applied to evaluation of safety and observational studies recently. Examples of such studies include a study[17] merged with RCT suggesting safety issues that nifedipine, a Ca antagonist, may increase risk of death dose-dependently, which was carried out as the secondary prevention study of coronary artery diseases, and studies[18), 19)] of merged analysis of multiple observational studies concerning risk of breast cancer in oral contraceptives and hormone replacement therapies.

(2) Issues and actions toward improvement

Following remarks should be taken into account to apply meta-analysis to observational studies:

1) Excessive expectation for estimation of overall index which indicates relationship between a drug and an AE should be avoided.
2) Meta-analysis should be utilized for comparison of data between studies and analysis of different results due to various factors, rather than to estimate overall risk index.
3) A score to evaluate quality of studies should not be used for selection of studies to be included.

This is also applicable to intervention studies. It may be related to the ex post facto feature of meta-analysis.

Above 1 and 2 explain the possible risk that meta-analysis may merge results of analysis given in published literatures with stereotyped procedures and merged result is considered as absolute truth. It means that when similar results are merged, the merged result would be estimated as a matter of course. Points to be considered are regional difference of the subject population in studies, differences in results according to sub groups, and issues insufficient as evidence which require further study. When homogeneity/heterogeneity of methods and results by individual studies are carefully examined, deeper insight about study objective and result could be obtained compared to a single study, and important suggestion could be provided to future study plan.

Meta-analysis retrospectively utilizes preexisting studies, and for PMS, which gradually accumulates appropriate use information, it has greater significance in prospectively deciding the direction of future studies. With regard to merger of published literature, the analysis mentioned in 2) above tends to be insufficient, but, when researchers who conduct the studies combined their raw data together, significant analysis to determine future direction of the study is available. Ideally, investigators' groups would proceed their own studies by placing meta-analysis in between.

3) mentioned above is related to the issue of selection bias. Publication bias that unpublished study result can never be obtained has been always pointed out. 3) mentioned above is also related to issues of evaluation bias. If selected studies include only studies having good quality, new bias may occur. US Preventive Services Task Force has discussed this issue[20].

If there is a trend that studies which resulted in unexpected results did not meet expectation or ended incompletely with unclear results are scarcely published, it may cause publication bias. It is difficult to solve such issues which are affected by the conscience of investigators and sponsors. Cause of the

incomplete result lies in quality of individual studies but not in the meta-analysis (See Section 5 and 10 of Detailed Discussion), and it should be traced back to planning phase of individual studies such as patient numbers.

Issues of publication bias are especially significant in safety studies for which transparency is required. Meta-analyses have been carried out mainly to clarify effects of pharmacotherapies, but the method should rather be used to evaluate safety information in the studies of less frequent AEs. To utilize the method to evaluate safety, it is necessary to standardize safety data including AEs in each study, and to widely publish the study results.

When quality of studies is the issue concerning 3 above, sensitivity analysis to examine change of the merged results, when selection range was changed, may be possible, but it is retrospective. When the group of investigators conducts studies of good qualities prospectively, and brings standardized data together, it would be effective measures for selection bias.

(3) Perspectives

Concerning anti-hypertensive drugs and anti-platelet drugs, meta-analyses have been carried out in foreign countries, and such studies have affected on the use of drugs in Japan, but the meta-analyses scarcely include Japanese studies. It is obvious that caution is required in terms of differences in drugs, dosages, and ethnic difference of metabolic enzymes to evaluate overseas study results in Japan. Fundamentally, it is unreasonable to use merged results which do not include Japanese data and many useful studies should be conducted in Japan regardless of issues concerning meta-analysis.

When Japanese studies increase, the data could be included in overseas meta-analyses. It is also possible to conduct meta-analysis using Japanese data or data combined with overseas data in Japan. Meta-analysis taking care of the issues 1), 2) and 3) in (2) above is important method to seek evidence in PMS, and it should be applied to safety studies. Quality of the studies can be improved by merging studies, and it may progress standardization. Feed back between individual studies and meta-analysis may contribute to development of PMS.

12. Issues on ethical principles

The Declaration of Helsinki includes ethical principles of medical studies such as prevention of health hazards of subjects including patients, protection of dignity, rights and privacy of individuals. ICH-GCP discusses principles of clinical trials with drugs.

These principles are related to individuals, but PMS which aims establishment of appropriate use of drugs has public ethics such as feedback to national health services. Ethical issues of PMS lie in the points between the aspects to provide precise information to society and to protect individuals. It means that it is the premise to consider individual ethical issues that the study objective necessary for appropriate use should be selected, the study is planned and implemented with scientifically sound methods, and the result should be publicized or disclosed.

(1) Current situation

In Jun 2002 "Ethical guideline of epidemiological studies" of MECSST and MHLW was enforced. Expert committee of clinical studies is discussing "Ethical guideline of clinical studies" While the principle of PMS has not yet been established, when the study methods are categorized into epidemiological observational studies and intervention studies according to Section 5 of Detailed Discussion, ICH-GCP or ethical guideline of clinical studies could be applied to clinical trials. When ethical guideline of epidemiological studies are applied to PMS observational studies based on pharmacoepidemiology, characteristics of pharmacoepidemiology or PMS should be considered discussed as follows:

(2) Nature of PMS compared with other epidemiological studies

Primary target of Ethical guideline of epidemiological studies is considered to be prospective regional cohort studies, and case control studies concerning outbreak of some disease. Focuses of these studies are risk factors such as lifestyle, are risk factors such as life style, environmental factors or genes. Major concern of a clinical epidemiological study collecting hospital information of multiple site is efficacy of a treatment or long term prognosis.

On the other hand, for PMS, such as prospective pharmacoepidemiology studies with marketed ethical drugs and pharmacoepidemiology studies using database, it seems that ethical guideline of epidemiological studies is not intensely considered. Risk factors which PMS handles are marketed drugs which are subject of regulation. It has following characteristics compared to the above common epidemiological studies:

- The marketed drugs, which is a risk factor, could be withdrawn from market with the discretion of regulatory authority.
- Exposure to the risk factor may occur when specialists of physicians who expect effects intentionally prescribe or administer the drug.
- Marketed drugs, which are risk factors, are commonly prescribed within the frame of national health insurance in Japan.
- The guideline specifies the informed consent is not necessary for observational studies where only existing data is used. The concept of "existing data" is often ambiguous in PMS. Data in database is, of course, existing, but data collected in routine examination in prospective PMS and in drug compliance instructions from dispensing pharmacies can arise even if the PMS is not conducted, therefore such data may be considered as existing data.
- PAL revision made the ADR reporting obligatory to health care professionals.

Discussion of ethical committee and protection of private information such as names, birth dates, sex and address, etc should be handled with caution as same as those in common epidemiological studies. Anonymity without linkage is preferable in database. Anonymity with the link of unbiased person is considered appropriate in studies having possibility of follow-up examination.

(3) Recommendation

It is recommended to specify ethical principles in conformity with "Ethical guidelines for epidemiological studies" as follows:

1. While case control studies with control arm of general population require consent from individuals, activities and studies for safety surveillance such as spontaneous reports and signal detection, prospective cohort studies, and studies using database do not require consent from individuals.
2. Ethical committee should be required, but it is not required for studies conducted with different drugs in similar system.
3. Concerning 1 and 2 above, "Ethical guidelines for epidemiological studies" is requested to be revised. Exception for disease based system such as cancer and additional description to avoid inconsistency should be considered.
4. "PMS guideline" should be prepared in conformity with the ethical principles and scientific rules in Section 5 of Detailed Discussion.

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