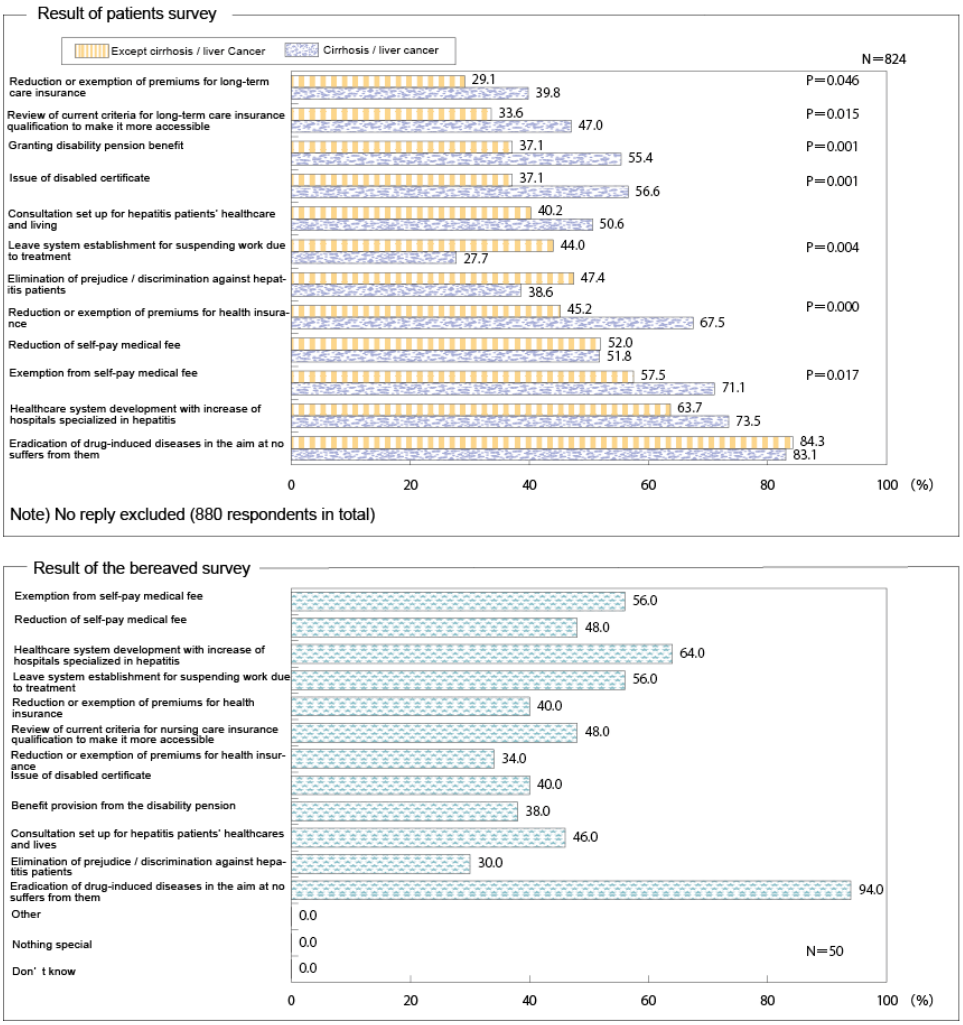
Section 2

Measures for the drug-induced hepatitis cases

The survey on actual situations of patients and the bereaved suffering with drug-induced hepatitis (collected: 880 patients, 54 bereaved relatives) which was made by the study group for the “Examination and Study on Hepatitis caused by use of Hepatitis C virus-tainted blood products and Prevention of the Recurrence” (a study group on the fiscal 2008 and 2009 Health and Labour Science Research Grants, Representative: Tatsuya Horiuchi, the president of the Society of Hospital Pharmacists, hereinafter referred to as the Study Group on Examination) is concerning what they hope for permanent countermeasures in future medical service and life security.

The result was the "eradication of drug-induced diseases" ranked highest, followed by establishment of the medical system, elimination of prejudice / discrimination and others (Fig. 2-2-1). The Ministry of Health, Labour and Welfare took the thoughts of suffers and has been making efforts on relief works for suffers and recurrence prevention such as realization of the proposals from the Study Group on Examination and enhancement of hepatitis measures.

Chart 2-1-1 Requests Regarding Permanent Countermeasures from Patients and the Bereaved Suffering with Drug-induced Hepatitis



1 Relief of Suffers from Hepatitis C Infection

Pursuant to the provision of the “Act concerning Special Measures to the Payment of Benefits to Relief Suffers from Hepatitis C Infection caused by Specific Fibrinogen Products and Specific Coagulation Factor IX Blood Products”, benefits has been provided to the suffers of Hepatitis C infection caused by specific products upon judgment by the court (As of July 1, 2010, compromises have been concluded with 1,519 people, and benefit has been provided to 1,463 people).

As part of ongoing efforts, the Ministry of Health, Labour and Welfare has encouraged the people who were possibly administered fibrinogen products or Coagulation Factor products to take Hepatitis virus screening by disclosing the names of the medical institutions that the products were supplied to and has publicized the concept of the Act.

Chart 2-2-2 Framework of Relief of Suffers from Drug-induced Hepatitis C Infection

<1> Products Involved

[Fibrinogen Products]

Name of Product	Date of Approval
Fibrinogen –Bbank	June 9, 1964
Fibrinogen – Midori	October 24, 1964
Fibrinogen – Midori	April 30, 1976
Fibrinogen HT – Midori*	April 30, 1987

[Coagulation Factor IX Blood Products]

Name of Product	Date of Approval
PPSB – NICHIYAKU	April 22, 1972
Konyne	April 22, 1972(*)
Christmassin	December 27, 1976
Christmassin – HT (*)	December 17, 1985(*)

(*) Limited to the products heat-treated for virus inactivation

(The mark "*" means import approval, others do manufacturing approval.)

<2> Contents of Benefit Payment

(1) Three categories based on symptom

	Symptom	Benefit
①	Those with chronic hepatitis C are affected with cirrhosis or liver cancer or dead as hepatitis C developed.	40million yen
②	Those who are affected with chronic hepatitis C	20million yen
③	Those who does not fall into the category ① or ② (so-called "no-symptom carrier")	12million yen

(2) If the symptom further develops in ten years after benefit receipt, an additional benefit is paid based on the doctor's certificate.

(The benefit amount is paid as "additional benefit", subject to deduction of the previously paid benefit from the benefit amount of the currently applicable category.)

<3> Eligibility Requirement

If the person is affected with Hepatitis C caused by use of a product shown in the <1> and has a symptom shown in the <2>, whose case reached judicial settlement, compromise or conclusive judgment, the said person or his/her heir is eligible for relief benefits.

<4> Deadline for Claim Submission

No later than January 15, 2013

(However, the cases of being under judicial judgment at the time of January 15, 2013 will be claimable within one month after judicial judgment.

<5> Consultation Counter

Pharmaceuticals and Medical Devices Agency

Free call 0120-780-400

(Open hours: 9 a.m. – 6 p.m. Monday to Friday (except national holidays and the New Year's Holiday)

*Pharmaceuticals and Medical Devices Agency

Website (relation information

http://www.pmda.go.jp/kenkouhigai/c-kansen.html

2 Prevention of Recurrence of Health Hazards Caused by Drugs

The "Final Proposal" (April 28, 2010) was made upon consideration of repeated amendments done to the administrative system, which suggests a fundamental review of the pharmaceutical administrative organization. The Ministry of Health, Labour and Welfare

is making efforts based on the proposals that were suggested in the “Interim Summary (July 31, 2008) and the “First Proposal” (April 30, 2009) by the Study Group on Examination as described hereinbelow. As for the “Final Proposal”, the Ministry of Health, Labour and Welfare took it into consideration sincerely and undertake steps from the achievable matters promptly and steadily.

(1) Efforts Based on the “Interim Summary” by the Study Group on Examination

The “Interim Summary” (July 31, 2008) of the Study Group on Examination incorporated and summarized the matters concerning the basic posture of pharmaceutical administrative organizations, importance of post-marketing safety measures, and current situation and problems in post-marketing safety measures. As the measures requiring prompt implementation, 1) improvement / enhancement in collection, analysis and evaluation of safety information, 2) introduction of new analysis /evaluation methods and new risk management methods, 3) urgent and substantial increase on the number of personnel in charge of safety measures were raised.

These proposals were used for securing a budget in fiscal 2009 to increase the personnel relating to safety measures by 100 staffs in the Pharmaceuticals and Medical Devices Agency (PMDA) (Chart 2-2-3), and to implement the following tasks.

・Investigations so to grab the actual situation when an attached document*1 was ordered the marketing authorization holders of pharmaceuticals and medical devices to revise, such as whether the information of the revised contents are adequately known to and applied to the medial work fields

・Investigations on the system accumulating the severe cases of adverse drug reactions for searching genetic polymorphism (biomarker) *2

・The study of management plans for risk minimization by dividing roles among the marketing authorization holders of pharmaceuticals, medical staff, patients and the national government (to study the safety management for post-approval from the stage of approval review)

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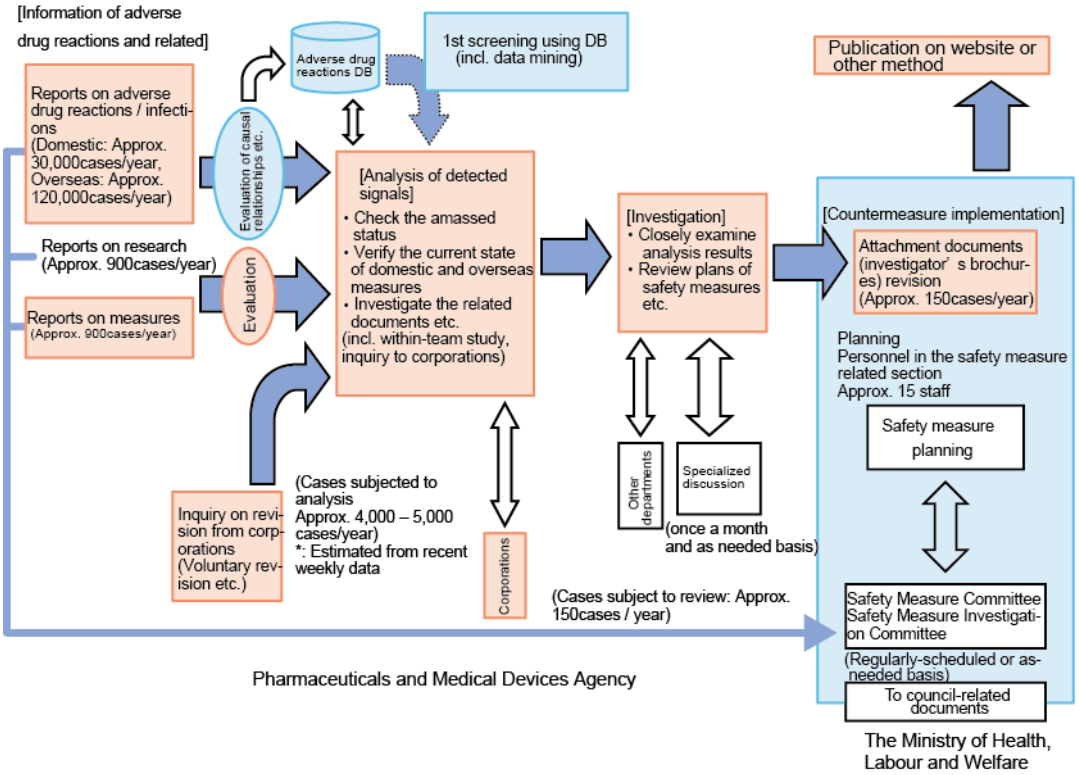
*1 A document compiled for doctors, dentists and pharmacists about the efficacy, dosage & administration, and other precautions (including contraindications, drug interactions, and adverse reactions)

*2 The individual difference in the sequence of DNA forming genes, which can be a trigger for adverse reactions or other diseases.

Chart 2-2-3 Workflow of Pharmaceuticals Safety Measures



(2) Efforts based on the"First Proposal" of the Study Group on Examination

The "First Proposal" of the Study Group on Examination raised concrete contents concerning reforms of pharmaceutical administration with the aim of prevention of any recurrence of suffering to people's health caused by drugs. In response to the proposals, the Ministry of Health, Labour and Welfare is promoting necessary measures successively as introduced below; for instance 1) measures on fiscal 2010 budget, 2) Measures by the Health and Labour Science Research, 3) Measures by the Pharmaceuticals and Medical Devices Agency (PMDA).

1) Measures on the Fiscal 2010 Budget

The measures on the fiscal 2010 budget*3 in response to the "First Proposal" are shown in Chart 2-2-4, which covers wide-ranging proposals comprehensively.

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*3 This includes only the items that were budgeted for, excluded those reflected as policies or points to remember in the ordinary duties.

Chart 2-2-4 Response Actions with the FY 2010 Budget

Suggestion of the "First Proposals" (abstract)	Response actions with FY 2010 budget
"Lifelong study concerning adequate use of pharmaceuticals is necessary for doctors, pharmacists, dentists, and nurses with the aim of prevention of incidents or health damages caused by drugs" (p.25) "Adequate manpower of pharmacists need to fostered and secured enough to transmit information on medical safety assurance, as well as to support patients with the aim at early detection of adverse reactions and occurrence prevention in tandem with doctors" (p.38)	Provide a pharmacists' on-site training at hospitals / pharmacies making active efforts in team medical care and local healthcare. 21million yen (new)
For occurrence prevention of incidents and health damages caused by drugs, not only in the professional education but also in elementary and secondary education health damages caused by drugs / medical devices needs to be learnt to understand relationships with pharmaceuticals. (p. 25)	Develop educational materials targeted at junior high school students on harmful effects of drugs. 13million yen (new)
In response to the past events of harmful drug effects caused by inappropriate off-label use, off-label use should have applicability under agreement of patients only to an extent where its advantage is assured with evidence. (p. 29) "In the case of applying off-label use when needs in clinical practice as well as safety and effectiveness are evidenced, as a premise for the patient's will and doctor's judgment, systems required in health insurance treatments should be developed immediately and eventually the whole structure should be well organized based on appropriate approval procedures." (p.29-30)	Open review meetings for unapproved pharmaceuticals / off-label use highly required in clinical practices (intended to reach a solution by approving them). 63million yen (new) Increase the number of judges of PMDA to place the highest priority on domestic unapproved pharmaceuticals. 959million yen (ongoing)
"As for safety measures for post-marketing use of pharmacogenomics, research and study should be promoted toward realization of it. To detect types of patients likely to be affected by adverse reactions at high risk or such, multidirectional and cross-sectional analysis and evaluation should be made systematically and constantly." (p. 31)	Make foreign market research to aim at improving data amassing method and strengthening the preventive measures on adverse reactions. 14million yen (ongoing)
"In the pharmaceutical administrative organizations, team structures consisting of professionals from medicine, pharmacology, pharmacoepidemiology and biostatistics etc. are required in line with characteristics of respective medical fields as a risk management function based on precautionary principals." (p.31)	Increase and normalize the personnel (47 staff) related to safety measures in the Pharmaceuticals and Medical Devices Agency and take related approaches 520million yen (ongoing, budget increased)
"The Ministry of Health, Labour and Welfare should clarify the procedures in revision of approved contents about efficiencies etc. and directions to pharmaceutical firms about implementation of necessary tests in line with a report of adverse drug reactions or infections or a literature report." (p. 30)"The 'risk minimization project (tentatively called)' should be adopted promptly. (Skip) From the stage of approval decision, plans for key items and methods etc. of post-marketing risk management should be formulated. After approval it should be implemented properly, and necessary review for this project and publication of its contents and processes should be offered." "According to features of each pharmaceutical, risk management should be conducted in combination of appropriate methods. (Skip) As to pharmaceuticals subject to strict risk management, patients who the said pharmaceuticals are administrated to should be recorded by the pharmaceuticals firm as uniform management to check the safety measures status, and also evaluation and improvement systems should be established. ""As a first step these should applies to new products as well as approved products on as-needed basis." (p. 32)	Collect and study the necessary information toward adoption of "Risk minimization project / management system" (tentatively called). 11million yen (new)
"With the aim of transmission of further multidirectional information focusing on adverse drug diseases or such should be considered." (p.34)	Create or revise the manuals responding to patients who are affected by serious adverse drug reactions. 37million yen (ongoing)
"Concrete steps for effective transmission of information toward public and medical staff should be surveyed and studied to take them in." "To enhance provision of updated information (most recent findings on adverse drug reactions etc.) or necessary safety measures from pharmaceutical industries to safety management staff of medical institutions, and to disseminate the transmitted information through clinical sites in medical institutions, the government should give necessary instructions to them." "The actual status of implementation of safety measures in pharmaceutical firms, such as whether they unfailingly transmit necessary information to medical institutions, should be verified." (p. 34)	Survey the actual situation of information transmission to the safety management staff and information utilization in the medical institutions. 15million yen (ongoing) Survey the actual situation of information transmission from pharmaceutical firms to medical institutions just after new products being marketed. 12million yen (ongoing)
"Verifications (Skip) about ministerial ordinances of GQP (concerning quality control standards) and GVP (concerning post-marketing safety management standards) which are approval requirements of pharmaceutical industries (Skip) are handled by prefectural pharmaceutical inspectors, but national cares are also necessary for enhancing qualifications and assuring personnel." (p.36)	Strive to ensure consistency with international rules (enhance the quality of municipalities' inspection sections). 2million yen (new)
"With regard to the domestic use of unapproved pharmaceuticals that are personally imported, usage situations and necessary information should be collected through drug monitoring certificates and be compiled into a database for publication." "As to information cautioning adverse reactions of unapproved pharmaceuticals that are personally imported, prompt and widespread dissemination should be promoted when needed""(Skip) Because some of pharmaceuticals and quasi-pharmaceutical products personally imported are not proven in safety and effectiveness, (Skip) efforts to alert the public should be made." (p. 36)	Provide alerts based on the actual situations known from drug monitoring certificates. 15million yen (ongoing, budget increased) 15million yen (ongoing, budget increased)
"Centering on the persons in charge of safety management (Skip), further efforts for safety measures should be made. An example method for it is the information transmitting service (push e-mail) provided by the Pharmaceuticals and Medical Devices Agency, and registration to it needs to be enhanced." (p.37-38)	Study the method of providing information to clinical sites and promote utilization of push e-mail. 17million yen (ongoing)

*The stated budget amounts are rounded to the nearest million yen.

Producing materials for learning drug-induced hazards

According to “the final proposal” 1 of the Verification and Investigation Committee and to the voice from the drug-induced health hazard sufferers organization, claiming improvement of the education to prevent drug-induced hazards, the Ministry of Health, Labour and Welfare has appropriated budget to produce/distribute materials on drug-induced hazards targeting junior high school students in FY2010.

Children often find medicine in pharmacies/drug stores and on TV commercials and they sometimes become patients, requiring medicine.

Although you may appreciate the potency and efficacy of medicine when your fever drops and a cough are relieved after taking it, it is necessary to realize that there are unavoidable side effects even if you follow the directions and the dosage of medicine, and that there may be stronger side effects if you do not follow the directions.

It is expected to cultivate knowledge about drug-induced health hazard prevention, to eradicate discrimination against victims, and promote understanding about the social responsibility of companies, the administration and citizens by learning about drug-induced hazards and the actual situation of the health damage.

On the basis of the above, education materials are to be produced to diffuse an accurate knowledge among children by holding a study group with victims in FY2010.

On the other hand, it is required to have profound knowledge of drug-induced health hazards if involving in works relating to pharmaceutical products in the future. Learning of the history of drug-induced hazards is effective to understand the importance of paying careful attention to safety at manufacturing, selling and using medicines, and also understand the responsibility of those involved in medicine related service.

As for the education for pharmacists, subjects relating to drug-induced health hazards are positioned in the “Model Core Curriculum for Pharmaceutical Education” that is the guidelines for education at the college of pharmacy.

The Pharmaceutical Affairs was revised in 2006, under which the system for registration of sellers of the category Ⅱ OTC drugs and the category Ⅲ OTC drugs” has been introduced, and the opportunities of learning about the drug-induced health hazards have been secured for specialists engaging in selling pharmaceutical products, while “history of drug-induced health hazards” is introduced as a subject of the examination conducted by governors to confirm their quality.

Model Core Curriculum for Pharmaceutical Education (extracted)

(The Conference for Studying the Pharmaceutical Education Curriculum of the

Pharmaceutical Society of Japan (Corp) in August, 2002)

B Introduction

(1) Invitation to pharmacology

【Point of contact between the contemporary society and pharmacology】

Goal:

3 Be able to outline the background of a drug-induced hazard citing a concrete example

C Specialized education of pharmacology

C17 Developing and producing pharmaceutical products

(1) Workflow of development/produce of pharmaceutical products

[Drug-induced health hazards]

Goals

1) Explaining the cause and the social background of major cases of drug-induced health hazards (thalidomide, SMON, untreated blood products, Sorivudine, etc.) and discussing about methods to prevent them (knowledge/attitudes)

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1 “The final proposal” presented in April 28, 2010 pointed out the necessity of a discussion about that drug-induced hazards should be carried out not only as specialized education but also as a subject of elementary, secondary and lifelong education, and the necessity of promotion of pharmaceutical education for all citizens as well as measures to raise social awareness about it.

As for the medical fee revision from April, 2010, the following measures are promoted.

Chart 2-2-5 Actions under the 2010 Medical Fee Revision

Suggestion of the "First Proposals" (abstract) Response actions	Support by raising medical fees
"At the pharmaceutical committee and pharmacy sections in medical institutions, (Skip) from the view of health damage occurrence and harmful drug effects proactive efforts should be made to take certain role." (p.37) "(Skip) the pharmaceutical information sections should collect / evaluate the information related to medical safety assurance (attachment documents, data of recent pharmaceutical findings, information of adverse drug reactions etc.), and by system development the result should be conveyed to the clinic sites accompanied by pharmacists to check." " To avoid missing important information due to too much information burdening only doctors, (Skip) safety information management should be controlled by team medical care." (p.38)	Expand the "Supplement points for medical safety measures" Raise the point of the "supplement for medical safety measures (full-time working medical safety manager)" from 50points (500yen) to 85points (850yen), and add a new category, 35 points (350yen), as "supplement for medical safety measures (assigned medical safety manager)" with the aim of easing requirements and keeping the quality so to facilitate the medical safety measures in more hospitals. Add a new category "supplement for pharmaceutical safety information management system" : 50points (500yen) If the medical institution was equipped with a structure capable to take necessary steps promptly where the "pharmaceutical information management office" grasped the usage situations and important information on pharmaceuticals' safety, and if the said medical institution gave the "pharmaceutical instruction" to patients, the medical fee is to be supplemented by 50points (500yen) and to be paid from health insurance to the medical institutions.

2) Measures by the Health and Labour Science Research

The proposals include some matters concerning a system that has not been adopted in Japan and issues to be undertaken along with voices from the practical field relating to pharmaceuticals and medical devices or based on the research by professionals or such. These research are mainly conducted as a frame of the Health and Labour Science Research (Chart 2-2-6, 2 (2) 2), Section 2, pp46, 47), and several study groups consisting of great number of experts are making an effort to collect information on scientific knowledge for prevention of any recurrence of people' health caused by drugs, which outline are mentioned below.

Chart 2-2-6 Measures taken by Study Group

Suggestion of the "First Proposals"(abstract)	Measure taken by Study Group
"If the requirements necessary for approval were changed after approval, and the approved contents need to be reviewed, measures such as re-evaluation should be applied." (p.27) "With reference to the system in the Europe and America, positioning of approval (for package inserts) should be reconsidered so to clarify the administrative responsibility as official documents and to examine how to instruct the pharmaceutical industries." (pp.28-29) "(Concerning reevaluation) deadline should be set to limit the periods for submission of investigation / trial results and for disproval after unofficial announcement." "If necessary trial results were not submitted and a certain period elapsed from the beginning of reevaluation, the drug efficacy etc. should be deleted automatically." (p.30)	(Study title) Fundamental study for speeding-up of pharmaceutical screening by enhancing international harmonization on pharmaceutical regulations (Outline) Collect information of legal reasons and operation situations about the pharmaceutical reevaluation (renewal of approval) system in the Europe and America, and examine the legal position of package inserts to organize fundamental information for considering our nation' s system.
"There is criticism that the alerting function toward clinical sites is not working enough, methods of providing safety information including procedure guide for package inserts should be reviewed overall." (p. 29)	(Study title) Research concerning modalities of pharmaceutical package inserts and procedure guide (Outline) Reevaluate and reconsider the rule for pharmaceutical package inserts about items listed and order etc. for ease of use from the view point of doctors and pharmacists so as to modify them based on clinical practices and to make them updated to current medical progress, IT technology advance and patients' consciousness.
"A structure for utilizing information from patients (patients reporting system on adverse reactions) should be established. (Skip) because it can be assumed that clinical information is not stated as detailed as necessary for analysis / evaluation, an effective collection method of detailed clinical information by enhancing medicine counseling should be considered." (pp30-31)	Study title) Investigative study concerning measures to collect information of adverse drug reactions from patients (Outline) Research domestic and abroad actual situations of patients' reports on adverse drug reactions and consider the reporting form and database compiling / analysis method etc. with the aim of formulating an effective and efficient method how to collect information from patients and how to store / utilize it.
"Aiming at realizing post-marketing safety measures for pharmacogenomics*1, investigative research should be expedited. To detect patients' group at high risk of adverse drug reactions etc. multidirectional / cross-sectional analysis / evaluation should be made systematically and continuously." (p. 31)	(Study title) Research concerning genetics considerations etc. on genetic marker of drug-induced lung damage (Outline) Examine the common genetic background in cases of drug-induced lung damage caused by medications that is used for intractable diseases or cancer to scan candidate genes triggering lung damage, and research the mechanism underlying lung damage.
"In electronic Receipt data, patients remain anonymous in consideration of personal information protection, and administrative organs and researchers should be accessible in cases of investigation intended for a safety perspective. As for data provision for this purpose, cooperation of persons related to medical insurance needs to be encouraged. In addition, to increase the value of Receipt database the data needs to be cross-checked with medical records stored in medical institutions with due ethical considerations in cooperation with the persons involved." (p. 33)	(Study title) Study for pharmacoepidemiology database creation using Receipt etc. (Outline) Conduct searching analyses on overlapping medications or contraindicated concomitant drugs using anonymized Receipt data and on harmful symptom occurrences using drug usage information etc. to check the usability of the Receipt for pharmaceutical post-marketing safety measures.
Public administration, aiming at contributing to patients' safety, should strive to promote the measures as for certain pharmaceuticals with adequate involvement of specialized doctors and pharmacists, so that patients are given medications under their agreement and given adequate explanation.	(Study title) Investigative research on risk communication measures between citizens and medical staff about adverse reactions information: Consideration of effective information transmission method on adverse reactions (Outline) Research the effective provision methods on pharmaceuticals safety information in foreign countries between patients / consumer and medical staff, and consider the effective information transmission methods through sessions with mass media representatives.

*1) Pharmacogenomics: to analyze and evaluate the efficacy and safety of tested drugs retrievably and verifiably in clinical pharmacological trial and other clinical trial, using a method such as stratifying the persons being tested by screening of genome relating to pharmaceutical effects.

Chart 2-2-6 Measures taken by Study Group

Suggestion of the "First Proposals"(abstract)	Measure taken by Study Group
"If under the guise of press release or distributes articles of doctor' s interview or academic information pharmaceutical industries provide advertisement encouraging off-label use of pharmaceuticals in a practical sense, or provide exaggerated commercial message or offer information that give patients excessive hope to patients' association, it could disturb adequate use of pharmaceuticals, causing damage to expand. For prevention of it, public administration should supervise their information provision and commercial messages and also instruct them for high-quality MR education etc." (p. 35)	(Study title) Study on control measures concerning academic information provision with the aim of appropriate pharmaceutical usage (Outline) Conduct the domestic and international survey on actual conditions and regulatory situations concerning academic information provision by pharmaceutical industries to medical staff to consider adequate method of academic information provision.
Further efforts to familiarize the relief system on adverse drug reactions and infections caused by products derived from biological s ubstances are required. In parallel, relief coverage for patients unfortunately affected by health damage should be also considered such as coverage expansion to pharmaceuticals intended for cancer or other particular diseases, and to health damage to fetus. (p. 37)	(Study title) Research on modalities and operational improvement of the relief system to sufferers from adverse drug reactions (Outline) Grasp the actual conditions of system operations to prepare the study on modalities of the relief system.
"Pharmaceutical affairs council and pharmaceutical sections etc. in medical institutes should strive to take certain roles by collecting information / evaluating safety and effectiveness of information transmission and pharmaceutical use through objective eye for the prevention of health damage or drug-induced disorders." (p. 37) "In the aim of transmitting information on medical safety assurance and detecting early or preventing adverse drug reactions, necessary personnel of pharmacists should be secured and fostered in order to provide patients support." (p. 38) "The pharmaceutical information sections should collect / evaluate the information related to medical safety assurance (package inserts, data of recent pharmaceutical findings, information of adverse drug reactions etc.), and by system development the result should be conveyed to the clinic sites, accompanied by pharmacists to check it." (p. 38) "The safety information management including out-of-charge doctors and allied healthcare professionals like pharmacists should be adopted into team medical care to ensure thorough management." (p. 38)	(Study title) Investigative study for early detection and occurrence prevention of adverse drug reactions by pharmacists in team medical care (Outline) Examine the examples of successful team medical management of safety information in domestic medical institutes and pharmacies as well as abroad examples, and examine how to foster pharmacist capable to contribute to safety information management or adverse drug reaction prevention in team medical care.
In addition to these, the secondary use of clinical research data and Receipt data collected from hospitals or the like for pharmaceutical safety measures is to be discussed technically concerning the type and contents of database, technical tasks, personal information protection or ethics at the "Commission on approaches of utilizing healthcare-related database for pharmaceutical safety measure" and the results is to be summarized as proposals. At the "Panel on utilizing electronic clinical data for safety measures" (held in PMDA), quantitative evaluation of adverse drug reaction risk based on pharmacoepidemiological analysis by developing access infrastructure of electronic clinical information database, approaches to research actual conditions / efficiency of safety measures, compiling information of adverse reactions and usage results etc. into database and usage measure for Investigative research are now under consideration.	

3) Measures by the Pharmaceuticals and Medical Devices Agency (PMDA)

The Pharmaceuticals and Medical Devices Agency (PMDA) was founded in April, 2004 by merging three organizations: the former Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences that used to evaluate and approve the

pharmaceuticals and medical devices, the Organization for Drug ADR Relief Research that used to relate to relief of suffering from adverse drug reactions caused by pharmaceuticals, and the Japan Association for the Advancement of Medical Equipment that used to evaluate the medical equipment's identity, which also has a responsibility for a part of affairs concerning safety measures of pharmaceuticals and medical devices that transferred from the Ministry of Health, Labour and Welfare. PMDA handles three primary affairs concerning relief programs for suffers with health damages caused by adverse drug reactions or infections by bio-based products, evaluation of pharmaceuticals and medical devices pursuant to the Pharmaceutical Affairs Act, and the safety measures in these affairs, under the following philosophy.

Chart 2-2-7 Philosophy of Pharmaceuticals and Medical Devices Agency, Japan (PMDA)

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.
We conduct our mission in accordance with the following principles:

- ・We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.
- ・We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- ・We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- ・We play an active role within the international community by promoting international harmonization.
- ・We conduct services in a way that is trusted by the public based on our experiences from the past.

The matters promoted by PMDA in response to the "First Proposal" are as follows.

Chart 2-2-8 Measures taken by PMDA

Suggestion of the "First Proposals"(abstract)	Measure taken by PMDA
"GCP inspections should be stricter so that the Contract Research Organization (CRO), a specialized institute entrusting practical duties of clinical trials from pharmaceutical companies, does not issue data favorable for the pharmaceutical companies." (p. 26)	・Adopt a new style of evaluation step by step in which PMDA staff visit the company to check the reliability and conformity in cases of clinical trials for new pharmaceuticals. ・Enhance the cooperation with other countries in accordance with increase of international joint clinical trials.
"To ensure the screening quality, the current reviewing mechanism (at the Ministry of Health, Labour and Welfare, PMDA, municipalities) should be improved in quality by increasing necessary judges and training them based on the evaluation of current situations." (p.. 27)	・Implement the plan of personnel increase to 751 persons (max.) by FY 2013. ・Provide opportunities of training and interaction activities among Ministry of Health, Labour and Welfare, internal and external colleges and institutes continuously.
"As for addition of approval requirements, upon clarification of the contents and the period the review / trial should be done based on the requirements as soon as practicably possible and the results should be submitted promptly."	・Promptly conduct analysis / consideration in the case of no need for waiting for re-evaluation application.
Clinical trials and review should be promoted intensively and carefully to prevent reoccurrence of drug-induced diseases led by sloppy approval review even in the event of 2010 issue where the substance patent for major products expires causing new drug applications increases, or in the case of speeding-up of approval review for solving drug lag." (p. 28)	・Establish a structure toward improvement in quality of clinical trials and review. (the number of review teams to be doubled etc.)
"Of reports on adverse drug reaction etc. submitted by medical institutions, for instance, fatality / serious symptom cases a structure enabling public administration to investigate them, such as direct inquiries to medical staff involved in the said case, should be established with due consideration to personal information protection." (p. 31)	・Prepare for follow-up investigation on adverse drug reactions reports from medical institutions step by step from FY 2009. In FY 2010, carry out regarding entire reports.
"Team structures consisting of professionals from medicine, pharmacology, pharmacoepidemiology and biostatistics etc. should be established to enable to make judgment of safety information consistently at time of approval review and post-marketing stage by drug efficacy group in line with characteristics of respective medical fields." "The processes of information transmission and evaluation in team structure should be clarified to evaluate the effectiveness." "To improve promptness of detecting adverse drug reaction signals and to cover all of reported symptom, data mining should be promoted toward implementation and improved as needed in reference to cases of foreign countries." (p. 31)	・Increase the number of safety measure teams through several phases to aim at realizing team organization responding to review sections (about 12teams). ・Conduct close examination of whole reports about domestic adverse drug reactions / infections using IT technology etc. ・Carry out proactive utilization / continuous improvement of data mining technique for marshaling or evaluating / analyzing adverse drug reactions ・Standardize, propel the transparency and speeding up the processes from information obtaining on adverse drug reactions to safety measures planning including package insert revision etc.

Chart 2-2-8 Measures taken by PMDA

Suggestion of the "First Proposals"(abstract)	Measure taken by PMDA
"Efforts to allow medical institutions to easily discriminate the urgency / seriousness of the provided information should be made by conducting full-fledged review of the 'Urgent Safety Information' and 'Pharmaceuticals and Medical Devices Safety Information'" currently provided. In parallel, (Skip) the modality of information provision including message to public should be reconsidered."	・As to data of adverse drug reaction reports and investigation data on usage results, approaches to allow the persons involved to access for investigation / research from FY 2011 is now under consideration. ・Enhance the pharmaceuticals and medical devises information transmission service, and encourage registration to it (targeted at approx. 60,000 of registration by FY 2011, approx. 150,000 by FY 2013).
"If any possibility of problem arose, even gray–area information should be offered voluntarily to public and medical staff so establishment of a system for it is required." "As for information of adverse drug reactions or investigation data on usage results that are reported from pharmaceutical companies or medical institutions to administrative organs, a system enabling users to access and analyze the data should be established and patients' names remain anonymity in consideration of personal information protection." (pp. 33-34)	・Promote measures to facilitate ease of judgment on urgency / seriousness of provided information in the 'Urgent Safety Information (doctor letter)' and 'Pharmaceuticals and Medical Devices Safety Information'" .
"Efforts to propel transparency should be made, such as publicizing the documents stating reasons and process of safety measures." "In parallel with further dissemination of knowledge using the 'Drug guide for patients' , the utilization method of the guide should be considered to enrich it based on patients' needs."	・Provide the information concerning adverse drug reactions / troubled instances such as cases leading to revision of package inserts. ・Enhance dissemination of knowledge using "Drug Guide for Patients" and convenience of use of the guide. (Refer to p.42)

Chart 2-2-9 Efforts in Pharmaceuticals / Medical Devices Safety Information Provision

The Pharmaceuticals and Medical Devices Agency (PMDA) provides service to transmit information relating to safety of pharmaceuticals and medical devices, and is now striving to enhance it based on the "First proposals" .

[Information provision to medical professionals via e-mail]

By delivering e-mail messages to registered medical professionals and relevant people, PMDA proactively provides the safety information relating to the medical sites.

<Examples of provided information>

- Urgent Safety Information (Dear Healthcare Professional Letters)
  It is information to alert safety measures to be taken urgently, which is issued by pharmaceutical manufacturers at the direction of the Ministry of Health, Labour and Welfare.
- Pharmaceuticals and Medical Devices Safety Information
  It is safety information on pharmaceuticals and medical devices issued by the Ministry of Health, Labour and Welfare, which is compiled to disseminate once a month in principal.
- Directive Notification for Revision of Precautions (Pharmaceuticals)
  It is information of additional precautions in use of the pharmaceuticals under the direction of the Ministry of Health, Labour and Welfare given to pharmaceutical industries.
- DSU (Pharmaceutical safety measure information)
  It is complied once in a month by pharmaceutical industries for additional warning in use of pharmaceuticals.
- Recall Information Class I
  It is information of pharmaceutical specifications etc. with possibilities of causing serious health damage or death, which is selected from all of pharmaceuticals' recall.

Chart 2-2-10 Publication of Drug Guide for Patients

The "Drug Guide for Patients" is an explanation for patients and their family members, which helps them better understand prescription drugs, leading to earlier detection of serious adverse drug reactions. This guide is compiled in plain words based on package inserts directed to healthcare professionals, especially targeted at things to know prior to usage of pharmaceuticals by patients.
(http:www.info.pmda.go.jp/guide_ippan/guide.html)

<Examples of contents>

- What is this medicine?
  Sales name, nonproprietary name, and amount of active ingredient contained in 1gm
- What is the effect of this medicine?
  Effects, name of diseases subject to administration etc.
- Are there things to be aware before using this medicine?
  Patients not available for administration, patients available for administration with special care, encouragement of doctor / pharmacist counseling for concomitant medication requiring careful attention
- How is this medicine used?
  Dosage / dose frequency, how to take the medicine, responses to failure to take the medicine, responses to too much dose
- What are precautions while using this medicine?
  Serious side effects and major subjective symptom (by category of side effects, or body parts where symptom appears at)
- What is the shape of this medicine?
  Color, smell / taste, dosage form
- What is contained in this medicine?
  Active ingredient, additive
- Others
  How to store it, how to handle if the medicine was left
- Contact information
  Telephone number of manufacturer's customer support contact center etc.

(3) Measures Based on the "First Proposal" of the Study Group on Examination

The Study Group on Examination had discussions to follow up the progress situation of the measures taken by the Ministry of Health, Labour and Welfare and PMDA based on the "First Proposal" (April 30, 2010) and to deepen the point at issue that was noted in the proposal in and after fiscal 2009, and on April 28, 2010 the "Final Proposal" was compiled.

The "Final proposal" incorporated not only individual steps of development, approval and post-marketing safety measures of pharmaceuticals, ideal postures of the medical work sites, academic communities, and pharmaceutical industries, but also a suggestion regarding establishment of the third-party audit / evaluation organization, ideal postures of the pharmaceutical administrative organizations, the problems of its organizational cultures with the description of the summarized questionnaire results revealing that most of PMDA executive posts have come from the personnel of the Ministry of Health, Labour and Welfare. The outline of the final proposal is described in Chart 2-2-11. *4

In the "Final Proposal" there are several tasks which are not able to achieve without reforms to promote as whole government including the human resource cultivation, those without preparation of an adequate amount of budget, or those without cooperation of other

than government such as pharmaceutical industries, medical experts and researchers. The Study Group on Examination suggests that not only the Ministry of Health, Labour and Welfare as the whole government should promote issues of the proposals promptly and sincerely.

The Ministry of Health, Labour and Welfare re-acknowledge the preciousness of life and pledge to make its best efforts to prevent any recurrence of suffering to people's health by drugs or pharmaceuticals, and thus is to undertake steps from the achievable matters promptly and steadily taking these proposals into consideration.

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*4 The full text of the "Final Proposal" is available on the website of the Ministry of Health, Labour and Welfare （http://www.mhlw.go.jp/shingi/other.html#iyaku）.

Chart 2-2-11 Summary of Review of Pharmaceutical Administration for Prevention of Drug-induced Health Damage (Final proposals)

(Study group for Examination and Study on Hepatitis caused by use of Hepatitis C virus-tainted blood products and Pharmaceutical Administrative Organs for Prevention of the Recurrence)

[Gothic font: new items added to the "First proposals" (a sign "★" shows a major item)]

No.1 At the beginning

○The study committee is held to examine the drug-induced hepatitis cases and to suggest about review of pharmaceutical administrative organs with the aim of recurrence prevention.
○Progress of committee: 23times held from May 2009 to March 2010
○Contents: the results of deliberations added to the basis of the first proposals

No. 2 Problems extracted from the process of drug-induced hepatitis cases

○Problems extracted from the process of drug-induced hepatitis cases from the perspective of prevention shall be sorted out. [* identical to the First proposals]
(1)Progress-related of fibrinogen products
(2) Progress-related of coagulation factor IX products
(3) Fact-related through the said products
○**In FY 2009 following inspections to be conducted to sort out problems (★)**
(1) Hearings with administrative organs and pharmaceutical manufacturers involved in past events
(2) Healthcare professionals' consciousness survey (doctor questionnaire, doctor interview)
(3) Victims' current situation survey (patients survey, survivors survey)

No.3 Process of past major reviews in systems [* identical to the First proposals]

○Organize past major systemic revisions of pharmaceutical administration
・Pharmaceutical Affairs Law related
・Pharmaceutical administrative organs' transition related

No. 4 Review of pharmaceutical administration for prevention of drug-induced health damage

○Suggest a drastic review of pharmaceutical administration for prevention of drug-induced health damage
(1) Basic concepts
① Review in spirit of staff involved in pharmaceutical administration and in regulations ②Development of administrative organs' system and personnel involved in pharmaceutical public administration ③Education in drug-induced health damage / pharmaceutical evaluation ④ Establishment of Institute of research material on drug-induced health damage ⑤**Experts fostering and development of pharmacoepidemiological researches etc. (★)**

(2) Clinical study / clinical trials
(3) Approval review
①evaluation in safety / efficiency, ② **review procedure, neutrality / transparency of evaluation (★)** ③ package inserts ④re-evaluation
(4) Post-marketing safety measures etc
① Strengthening of information collection structure
②**evaluation of obtained information (adoption of new risk management method (★) etc)** ③ **proactive and smooth provision of information for risk communication improvement and involvement of patients / consumers** ④ information of adverse drug reaction conveying the said person and modalities of information disclosure, ⑤ adequate information provision and adequate usage of pharmaceuticals via advertisement ⑥ GMP investigation ⑦ GVP, GQP investigation ⑧ personal imports
(5) Safety measures in medical institutions
(6) Health damage relief system
(7) Effects to utilize professional knowledge effectively
(8) Fundamental sprits required for pharmaceutical companies (★)

No. 5 Future modalities of organizations in charge of pharmaceutical public administration

○**Organize discussion points on pharmaceutical administrative organs (★)**
・Discuss topics such as unification of pharmaceutical administrative organs (national government or public corporation). In this fiscal year, questionnaire survey about officials to be conducted.
・Despite organizational forms the modality of pharmaceutical administrative organs shall be suggested, for instance national government has responsibilities at the end.
○**The third-party audit / evaluation organization establishment (★)**
・To prevent occurrence and expansion of drug-induced health damage, a "third party organization" shall be established to audit and evaluate administrative organs involved in pharmaceutical administration.

No. 6 Closing comments

○To realize the proposals, there are opinions that **comprehensive basic Act concerning pharmaceutical public administration should be established**, which should be also considered.

Materials: Created by Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

3 Comprehensive Hepatitis Measures

The Ministry of Health, Labour and Welfare has made an effort to cope with sufferings with Hepatitis. For instance in recent years, the “Emergency Measures to Hepatitis C etc.” started fiscal 2002 and from fiscal 2007 appeals to prefectural governments for establishment of base hospitals for liver disease treatment have been made. In addition, from 2008, the “Hepatitis Aid Package” including hepatitis medical fee aid and free testing in the medical facilities entrusted by public health centers has started as comprehensive measures.

On the other hand, since there still are tasks to be solved in terms of early detection of hepatitis diseases and accesses to medical service, further efforts are necessary.

On November 30, 2009, the "Basic Act for Hepatitis Measures" was approved and established by the suggestion of the House of Representative, chairperson of Committee on Health, Labour and Welfare. This Act is aimed at promoting hepatitis measures comprehensively while it specifies the basic principal regarding the measures, clarifies the duties of national and local entities and establishes fundamental matters on development / enforcement of broad measures for hepatitis patients and persons infected with hepatitis virus so as to respect the human rights of them.

Besides, the Basic Act on Measures against Hepatitis prescribes that the Minister of Health, Labour and Welfare shall formulate basic guidelines on measures against hepatitis in line with comprehensive promotion. Toward this formation, the first council for promotion of measures against hepatitis was held in June, 2010.

Chart 2-2-12 Preamble of Basic Act for Hepatitis Measures

Today, there are a lot of people who are infected by hepatitis virus or affected by hepatitis in Japan, and hepatitis is the nation’ s top infectious disease.

Because hepatitis becomes chronic when it was left without appropriate treatment, possibly leading to serious diseases like cirrhosis or liver cancer, the anxiety of the said people for the future is immeasurable.

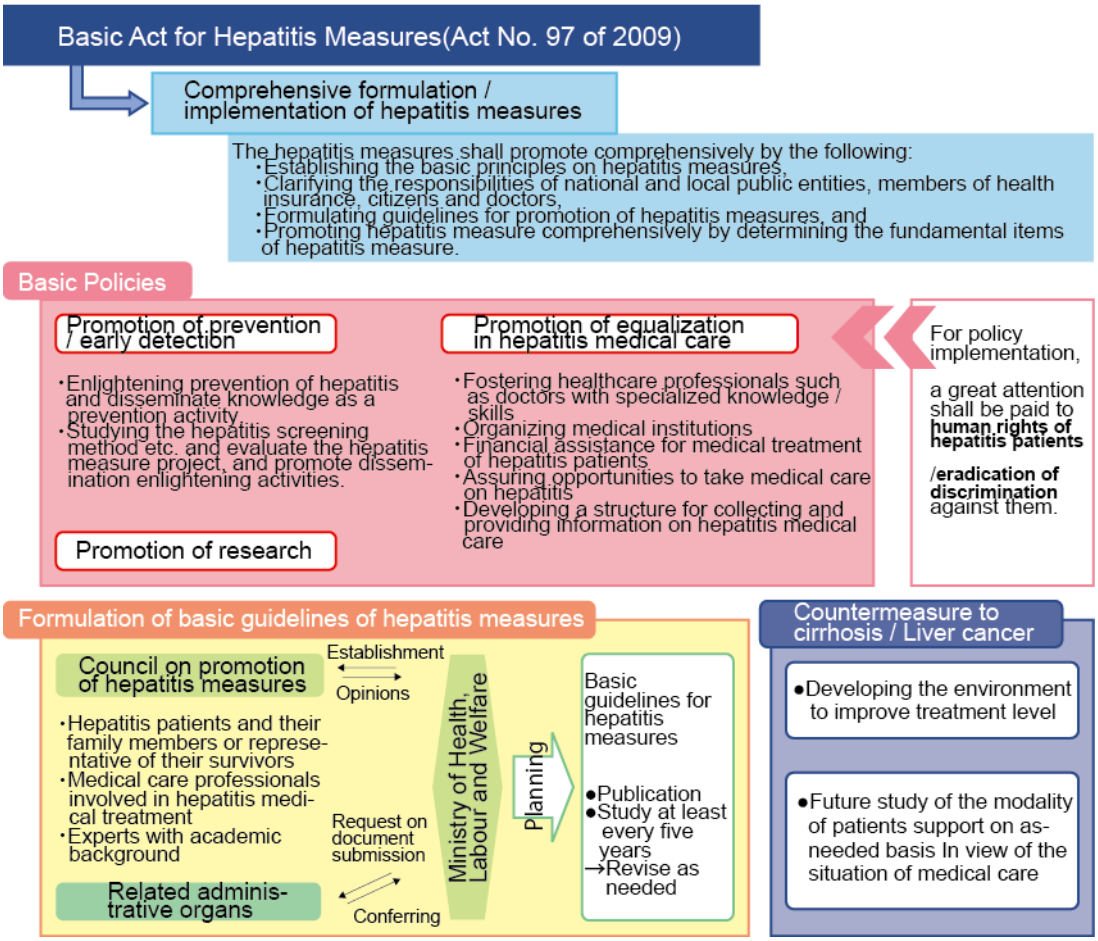
As a result of postwar medical advance, accumulated medical knowledge and progress in science technology the door for overcoming hepatitis disease is open, but on the other hand there are still a lot of tasks left in early detection and access to healthcare to cope with, and it is also a fact that correct understanding is not particularly entrenched in all citizens.

There are several cases of virus infection with hepatitis B and hepatitis C that were caused by the reasons attribute to national government’ s responsibility or by the reason of its cause not being identified. As for the drug-induced hepatitis case where specific coagulation factor products was contaminated with hepatitis C virus, causing infections among unspecified number of people, the government recognized its liability for that it caused great damage to the sufferers and could not prevent its spread, and as for the case of hepatitis B virus infections caused by vaccination shots where the syringes were repeatedly used at mass vaccinations, the government’ s liability for it has been proved by the final legal judgment.

In these situations, it is required that to promote further approaches to overcome hepatitis, such as to ensure provision of quality and adequate healthcare for sufferers from hepatitis virus and hepatitis patients, while guaranteeing respect for their human rights.

Clarifying the Basic Principles of the measures for hepatitis, we hereby establish this Act so as to promote the measures for hepatitis comprehensively.

Chart 2-2-13 Basic Act for Hepatitis Measures



(The History of Hepatitis Measures in the Ministry of Health, Labour and Welfare)

1) "Comprehensive Hepatitis Measures"（from fiscal 2008）

The Ministry of Health, Labour and Welfare has executed updated comprehensive hepatitis measures including medical fee aid from fiscal 2008. With the basic directionality of "early detection the hepatitis virus infection for prompt and appropriate treatment" and "to prevent more new infections by dissemination and enlightenment of correct knowledge on hepatitis and to develop an environment in which people suffering from hepatitis can live in relief", the concrete contents of the measures have five main approaches mentioned below.

❶ Environmental Development for furtherance of Hepatitis Treatment（Medical Fee Aid for Hepatitis Treatment）

As for hepatitis B and hepatitis C, the interferon treatment *5 and the nucleic acid analog drug treatment *6 are effective to prevent severer diseases such as cirrhosis and liver

cancer or to slow progress. However, though these treatments are covered with the health insurance, monthly out-of-pocket expenses or lifetime cumulative self-pay burdens will be high.

Therefore Ministry of Health, Labour and Welfare offers the aid program to relieve economic burdens of the hepatitis medical service cost with the aim of furtherance of prompt and appropriate treatment (the enforcement entities are the prefectural governments, subsidized half by national government).

This medical fee aid program is to reduce the monthly medical expenses based on income of the patient's household (annual residential tax). According to the Basic Act on Measures against Hepatitis and recent medical findings, the following three points has been improved on the fiscal 2010 budget for a more access-friendly system.

① Reduction of the maximum self-pay burden (monthly): In fiscal 2009 it was set at 10,000, 30,000 or 50,000 yen depending on the income, but in fiscal 2010 it has been changed to 10,000 in principal (as for the high income bracket, 20,000 yen).

② Expanded coverage for medical treatment: In fiscal 2009 only the interferon treatment for hepatitis B and hepatitis C was covered with the program, but in fiscal 2010, nucleoside and nucleotide analogues treatment for the hepatitis B has been added.

③ Relaxation of the package usage limits on interferon treatment: In fiscal 2009 the use for interferon treatment was limited to once, but in fiscal 2010 it has been changed to twice in the case satisfying a certain condition such as being recognized that interferon retreatment will be highly effective for medical reasons.

❷ Promotion of the Hepatitis Screening

In all prefectures and the cities with a public health center*7 and specified districts (136 in total), in consideration of user's accessibility, the hepatitis screening is provided at public health centers and medical facilities entrusted by them free of charge (survey in June, 2009). The actual hepatitis screening requires only blood test taking a short time, and the result will be informed within several weeks at the latest.

In addition to the operating system development for hepatitis screening, an approach to encourage people to have hepatitis screening has been taken by requesting and the affiliates of the Japan Federation of Economic Organizations to call in workplace and by doctors' approaches to visitors of the facilities with the cooperation of the Japan Medical Association, as well as concentrative call through the various media during the "Liver Disease Awareness Week" (the fourth week of every year May).

*5 Treatment by Interferon: Interferon reacts on and produces an effect on regulation of the immune system / inflation etc. which is significantly effective against proliferative actions of hepatitis virus. Interferon treatment is said to be effective for about 30% of hepatitis B patients and about 50%-90% of hepatitis C patients (the curative effect differs by genotype and quantity of hepatitis virus). In this treatment, severe adverse reactions such as "influenza-like symptom" of fever, headaches, muscular pains, "sleeplessness or depression", “hair loss", or "dizziness" tend to appear, and it is important to consult with a doctor before treatment.

*6 Treatment by Nucleoside and Nucleotide Analogues : Nucleoside and Nucleotide Analogues inhibit hepatitis B virus DNA synthesis and have an anti-proliferative effect against virus growth. Since discontinuing the use or resistant virus expression during dosage may cause exacerbation of hepatitis, it is necessary to consult with a doctor of a specialized medical service or equivalent about the treatment.

* The cities with a public health center, specified by the provisions of Article 5, paragraph (1) of the Community Health Act. In addition to the "ordinance-designated cities" and the "core cities" that are set forth in the Local Autonomy Act, seven cities such as Otaru city were designated individually based on regional situations etc.

❸ Patients Support Such As Upgrading of Medical Care System, the Training for Doctors etc, and the Consultation System Establishment

In the hepatitis treatment, as it is important to grasp the accurate condition of disease and to take adequate control of adverse drug reactions due to interferon treatment, a coordination network in individual regions between medical facilities specialized in liver diseases and medical facilities in charge of daily treatment as a private medical doctor is necessary to be developed for balancing the patient's work and treatment.

On this account, the Ministry of Health, Labour and Welfare is promoting the network centering on the "Base Hospital for Liver Disease Treatment" designated by prefectural governments.

In addition, the "Hepatitis information center" was held in the National Center for Global Health and Medicine with the aim of equalization and improvement in medical treatment by supporting information sharing between base hospitals, training for base hospitals and such.

Chart 2-2-14 Roles of base hospitals for liver disease medical care alliance

- Provision of general medical information concerning liver disease (to organize a counseling system for patients and carriers).
- Collection and provision of information on medical institutions etc. within the prefecture.
- Arrangement of workshop and lectures targeted at medical staff and local residents and Information assistance concerning liver diseases
- Setting up of consultative meetings with specialized medical institutions concerning liver diseases

❹ Dissemination and Understanding of Correct Knowledge through the Public

Since hepatitis is a common disease that many people has been affected or infected with, for prevention of more new infections with hepatitis virus and peace environment development for patients and infected persons it is important to disseminate correct knowledge about hepatitis throughout the public and to promote correct understanding of the disease. Therefore, the Ministry of Health, Labour and Welfare*8 and the hepatitis information center is making an effort to dissemination and enlightenment of correct knowledge via their websites and brochures with easy-to-understand terms*10.

❺ Efforts for improving therapeutic outcome on hepatitis are expected by many patients / infected persons and general public. The Ministry of Health, Labour and Welfare set an agenda in line with the "Seven-year Strategy for Hepatitis Research" complied in June, 2008 by the domestic experts of liver diseases and have been promoting the research from the basis to the clinical ground including development of new hepatitis treatment / therapeutic drugs.

2) Measures for the Revision of Medical Service Fee

On the revision of the medical service fee from April, 2010, the interferon treatment for hepatitis was evaluated in consideration of detailed explanation to relieve anxiety about the adverse drug reactions, and the coordination network development between specialists and the private medical doctors so that outpatients who need long-term treatment can go see a doctor continuously.

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*8 Ministry of Health, Labour and Welfare
（http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/index.html）
*9 Hepatitis Information Center（http://www.ncgm.go.jp/center/index.html）
*10 http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/siryou.html#poster

3) Positioning of Liver Dysfunction as the Physical Disability

Along with the matters agreed in the council between the plaintiff corps / legal counsel and the Minister of Health, Labour and Welfare in 2008, the Ministry of Health, Labour and Welfare has studied on positioning liver dysfunction as the physical disability. In October, 2008, the “Study Team on Evaluation of Liver Dysfunction” was formed, and seven times of conferences were held in total until August, 2009. The result was complied as a report presenting that the severe liver dysfunction persisting during a certain period falls under physical disabilities. On the basis of this report, physical disability certification standards was approved in the liver functional disorder held in September 11, same year, and according to this the Order for Enforcement of the Act for the Welfare of Persons with Physical Disabilities, the Order for Enforcement of the Handicapped Persons’ Employment Promotion Act and the related were amended, which went into effect on April 1, 2010.