Section 2

Drug-induced hepatitis incident

1 Lawsuit over drug-induced hepatitis and relief of hepatitis victims by the “Act on Special Measures for Relief of the Victims of Hepatitis C Virus Infection”

Since blood products are made out of human blood, there is possibility of infection caused by such products.

Therefore, the products must be strictly manufactured and managed.

Since Fibrinogen products *1 and the Coagulation Factor IX blood products *2 are manufactured out of human blood same as other blood products, there is possibility that those products include infectious risk such as hepatitis virus. In addition, inactivation has its limits in order to keep its function, so the risk of infection with hepatitis virus was always with those products.

Between 1971 and 1990, there were incidents that pregnant women were administered with Fibrinogen products or the Coagulation Factor IX blood products when bleeding to deliver their children, and they were allegedly infected with the virus included in the administered products. Then, patients filed a lawsuit against the government and the pharmaceutical industries seeking damages (hereafter the Lawsuit over Hepatitis C virus Infections) in the five district courts (Tokyo, Osaka, Fukuoka, Sendai, Nagoya) since October 2002, and all of them issued a ruling between June 2006 and September 2007.

Each district gave different rulings on the period of that the pharmaceutical industries and the government must bear responsibility for it and types of the products.

Then, the settlement discussion was made in the Osaka district courts and it was decided that reparations were made equally for all of them regardless of the period of administration by ”the Act on Special Measures concerning the Payment of Benefits to Relieve the Victims of Hepatitis C Virus Infections Caused by Specific Fibrinogen Products and Specific Coagulation Factor IX Blood Products”. (enacted January 11, 2008) (reparation overview: See Chart 2-2-2 in the section 2, Chapter 2 (40p))

With the enactment of the Act, the government acknowledged its responsibility for having caused crucial damage to the infected victims and failed to prevent the damage from outspreading according to the Basic Agreement between the plaintiffs and the counsel in the lawsuit on hepatitis C virus infection and the Ministry of Health, Labour and Welfare, and the Ministry apologized to the victims and their families as well as pledged to make their utmost efforts for prevention of drug-induced health hazards while renewedly respecting lives.

*1 “Fibrinogen” is a kind of protein in blood (blood coagulation factor) which is necessary for blood to clot. Fibrinogen products are produced through the process in which fibrinogen is extracted from the human blood, and refined products with a high purity are lyophilized to make “fibrinogen products”. Such products were used to use in many medical institutions when bleeding a lot and difficult in at delivery and surgery

*2 "Coagulation factor IX” is one of blood factor different from fibrinogen (coagulation factor I), and products which are separated and refined are mainly used for treatment of hemophilia.

Chart 1-2-1 Comment from the Ministry of Health, Labour and Welfare in the Signing Ceremony of the Basic Agreement for Settlement

Comment from the Ministry of Health, Labour and Welfare in the Signing Ceremony of the Basic Agreement for Settlement

January15, 2008

Today, I met with the plaintiffs and the counsel in the lawsuit on drug-induced hepatitis and signed the basic agreement for settlement.

I believe that the victims and the bereaved families of drug-induced hepatitis caused by Fibrinogen products and coagulation factor XI blood products must have gone through the long-standing tremendous hardship. We acknowledge that the government is responsible for the serious damage to the victims and the failure in preventing infection from spreading. We sincerely apologize to the victims and the bereaved families, and we would like to offer our sincerest condolences on your deceased family members and express deepest sympathy for those who are under treatment and their families.

“The Act on Special Measures concerning the Payment of Benefits to Relieve the Victims of Drug-Induced Hepatitis caused by Fibrinogen Products and Coagulation Factor XI Blood Products” enacted on January 11 after the bill passed both Houses.

On last December 23, the former President Yasuo Fukuda made a decision to resolve this issue by legislation proposed by the Diet members. Accordingly, the bill was enacted with the efforts by the concerned members of the ruling party, the cooperation and swift action beyond the factions, making way for resolution. We appreciate the efforts made toward the resolution, and we will keep working hard on the preparation in order to smoothly implement the payment of the benefits under the Act.
Besides, we will disclose medical institutions which purchased the said products, promote confirmation of patients administered the said products and advise them to take a hepatitis virus examination, and inform the public of the Act.

As we have pledged in the Basic Agreement, we will have talks with the plaintiffs and the counsel continuously while the third-party institutions are verifying the case.

Needless to say, we must never let this happen. Learning from this problem, we will take concrete measures to reform the pharmaceutical administration and to prevent a recurrence of such damage without forgetting about the loss of irreplaceable lives and hardship of the patients.

Your activities have moved the countermeasures against the hepatitis forwards. From the next fiscal year, we will promote measures including total 180 billion yen of a medical subsidy for the treatment with Interferon on the basis of “the Hepatitis Treatment 7- Year Plan” .

We would like apologize again to the infection victims for the long-standing suffering, and I , Minster of Health, Labour and Welfare, pledge to make every effort for preventing drug-induced damage, early detection of hepatitis, and improvement of the treatment system, respecting all lives.

2 Committee to verify the medical administration for investigation into the hepatitis C virus infection incident and prevention of recurrence

Through “the Basic Agreement” and subsequent discussions between the plaintiffs/the counsel and the Minister of Health, Labour and Welfare, the Ministry of Health, Labour and Welfare widely verified the occurrence of hepatitis C virus infection incident, the background of the outspreading damage and the cause of it, and held “Committee to verify

the pharmaceutical administration for investigation into the hepatitis C infection incident and prevention of recurrence” (hereafter “the Verification and Investigation Committee”) on May 23, 2008for the purpose of making proposals for advancing on the review of the pharmaceutical administration and preventing the recurrence.

In the beginning, the Verification and Investigation Committee was established to operate for only a year, however, it was extended for two years to complete the deliberations responding to request from the members.

First, on July 31, 2008, the results of intensive discussion on reinforcement of post-marketing safety measures as the urgent issue were aggregated as ‘the interim report’, and then, the issues on the basis of extracted problems from the hepatitis C infection incident were verified on and after October, and finally, "the first proposal” was made on April 30, 2009 as the goal of the discussion.

In FY2009, while the committee mainly focused on the issues needed more discussion in “the first proposal” in addition to the verification on the hepatitis C Infections, the committee announced “the final proposal” on April 28, 2010 with issues that had not been discussed enough in FY2008, and subjects needed to be deliberated.

In "the final proposal”, the committee has been proceeding the arrangement in response to each main process of the Fibrinogen products and Coagulation Factor IX blood products and on the basis of the facts relevant to both products including the facts in the past which seem to be problems from the present viewpoint for the purpose of reviewing pharmaceutical administration to make it never happen and discussing on how the organizations responsible for pharmaceutical administration should be from now on(See Chapter 2-2).

Also, to analyze why the Hepatitis C Infections occurred, the committee conducted hearing and survey to the administration, the organizations and concerned medical institutions which were involved in the incident at the time of occurrence. Besides, in order to disclose the actual conditions of the damage that the infected victims had, the committee has been attempting the survey to the victims and their families on the physical, mental, economical and social damage they have gone through.

Through the verification of the pharmaceutical administration, “the final proposal” points out that the system relating to the then system of the pharmaceutical administration (in a broad definition, it indicates direct regulations by the Pharmaceutical Affairs Act included in “the final proposal” the situation of performance of the organizations and the employees, organizational cultures, the medical profession, and the relationship with the pharmaceutical companies), was inadequate and the incident could have been prevented if the system functioned properly.

Moreover, the following are pointed out in “the final proposal” as “the basic philosophy required for persons engaged in the pharmaceutical administration” correlative to the review of the pharmaceutical administration” to prevent hepatitis C infections (chart 1-2-2). The Ministry of Health, Labour and Welfare must realize these basic concepts and must sincerely accept the proposal relating to the pharmaceutical administration correlative to preventive measures of hepatitis C Infections and make every effort to realize the proposal on the basis of the solid resolution of those engaged in the pharmaceutical administration such as the Pharmaceuticals and Medical Devices Agency *3, municipalities, medical institutes and medical personnel including doctors, pharmacists and dentists” and “if drug-induced damage unfortunately occurs in the future, the Ministry will address it without ruining a reliable relationship among all concerned including patients/victims and pharmaceutical companies.

Chart 1-2-2 The basic attitude required of those engaged in the pharmaceutical administration (*Excerpted from “the Final Proposal”)

• First of all, what we must focus on is to realize anew that the vocation of those engaged in the pharmaceutical administration (the government, the incorporated administrative agencies [1] and the local governments [2])is to protect lives and citizens’ health, and without making light of irreplaceability of human life, and to realize that swift decision-making on the basis of the principle that a preventive measure against the risks of insecurity is indispensable while doing our best to secure the safety and effectiveness of drugs with a high sense of ethics.

• Although the present pharmaceutical administration is apt to incline to the regulation on the medical products, the medical products can be effective by being used properly in the medical treatment. Therefore, it is necessary that those who are in pharmaceutical administration fully understand the situation of the obliged roll of the medical personnel such as doctors and pharmacists, and it is essential to cooperate closely with medical personnel and researchers, and to accomplish their duties.

• As analyzing and evaluating the side effects and others, it is important to keep the importance of the life in their mind without the prejudice and to evaluate on the basis of the latest scientific knowledge. Besides, since the medical progress accompanies uncertainty, it is necessary to predict the worst case, and to endeavor to plan/implement the safety measure according to swift decision-making with the responsibility of the pharmaceutical administration without waiting for the verification of the scientific hypothesis regarding the risks on the basis of the principle of prevention when it is predicted that there is a possibility of substantial health damage to patients. Especially, if the health damage of the patients is assumed as irreversible, the swift measure mentioned above must be implemented.

• To implement the evaluation of the information on the safety measures and the countermeasures, the following points must be considered to perform their duties.①Drug-induced sufferings may be caused by lack of provision of information on risks which the medical institutes and the administration had already known and by not implementing the appropriate measure/countermeasure due to the disregard of the information on the risks rather than caused by the lack of the knowledge of the latest information.②There are cases that the administration did not make its decision on the regulation due to misevaluation of the information they had.

[1] Indicates the Pharmaceuticals and Medical Device Agency (Incorporated Administrative Agency (PMDA))
[2]In “the Final Proposal” , expression for the safety and effectiveness of the pharmaceutical administration and that of the medical products including the medical instruments are applied.

*3 Stands for the Pharmaceuticals and Medical Devices Agency. It is an incorporated administrative institutions under the Ministry of Health, Labour, Welfare, and it was established by merging “the Pharmaceuticals and Medical Devices Evaluation Center of National Institute of Health Science (PMDEC)”, “the Organization for Pharmaceutical Safety and Research (OPSR/KIKO), and part of “the Japan Association for the Advancement of Medical Equipment (JAAME) ” in 2004.

3 Issues on the files of the Fibrinogen products

As for the related issue to hepatitis C virus infections, although the ministry disclosed files with masked names including the case list of 418 victims who contracted hepatitis after being administered fibrinogen products presented by the Mitsubishi Pharma Corporation (then), a fibrinogen products maker, the bureau in charge did not know that there was a file with real names unmasked had been in the basement storage of the Ministry of Health Labour and Welfare due to the inadequate takeover/management of the files, and the Minister answered the Diet that the Ministry didn’t have any information to specify the victims.

As a result of this, the Ministry has been criticized that it deliberately hid the information and neglected the duty to inform patients of their infection of the Hepatitis C Virus based on the files.

As for this issue, the project team composed of external attorneys and the Vice Minister of Health, Labour and Welfare, as the leader, to investigate into the Ministry produced the reports, and pointed out in the reports in the following chart.(chart 1-2-3)

Moreover, in "the final proposal” of the Verification and Investigation Committee, it is pointed out that “each employee is required to change their consciousness to keep considering the patients and the victims when performing the task of the Ministry of Health, Labour and Welfare which is responsible for protecting the citizens’ life and health besides the improvement of the file management" and “It is thought that some of the medical records of medical institutions were possibly disposed during the period of two years before the disclosure after completing the procedure of it, which seem to have affected digging for victims. *4 It is unavoidable for the Ministry to reform the attitude of the organization and that of each employee, and to speed up their decision making".

Measures for this issue:

・Implementation of notification of the fact that the product was been administered and that

of recommendation to take a hepatitis test for 418 patients who contracted hepatitis through the drug makers and medical institutions since October 2007

・Requesting about 7000 medical institutions which purchased the fibrinogen products and 2600 medical institutes which purchased coagulation factor blood products to notify those who are confirmed to have been administered of the said fact and advising them to take a hepatitis virus test in November 2007 and February 2008

Chart 1-2-3 Reports of the project team on the internal investigation (excerpt)

• According to the files of 418 persons including 2 files with real names obtained on the process of the investigation, with regard to their carelessness about the patients, we must sincerely take the criticism that we must consider about what we have to do for patients suffering from hepatitis from the perspective of citizens as the administration that have jurisdiction over the issues related to people' s life and health, rather than discussing on who should assume the institutional and administrative responsibility.

• In the first place, it is the serious issue that the officials concerned have lacked the basic and important concept such as "importance of document management for the administration" , and it is an important subject to be urgently addressed by not only the Pharmaceutical and Food Bureau but also all officials of the Ministry of Health, Labour and Welfare.

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*4 The said file was requested to be disclosed on the basis of "the Act on Access to Information Held by Administrative Organs" in December 2002.
In the beginning, the Ministry of Health, Labour and Welfare did not disclose the names of the medical institutions. However, it accepted the report advising "Disclosing the names (of the medical institutions) must be absolutely necessary" submitted by the Disclosure Examination Board of the Cabinet Office in response to objections, the Ministry agreed with disclosing not only a part of the medical institutions which reserved the products at that time but all institutions which purchase the products. It took long due to the procedure for disclosing information and requesting drug makers to disclose all institutions which purchased the products, therefore, the disclosure was realized after two years from then, in December 2004.

・In January and July 2008, the Ministry disclosed medical institutions which purchased the said products through notice in newspapers and the website of the Ministry, and advised people to take a hepatitis virus test.

・Also informing people about the system of benefit payment by the Special Relief Act on the website of the Ministry of Health, Labour and Welfare and through the said medical institutions

・The Ministry took measures for appropriate record keeping and management in order to improve the file management of the Ministry.

In “Emergency Information - notifying to take a hepatitis virus B and C test (about the disclosure of the medical institutions that purchased coagulation factor blood products)and advising to take a hepatitis C virus test (about re-disclosure of the medical institutions that purchased fibrinogen products) on the homepage of the Ministry of Health, Labour and Welfare website, you can see the medical institutions which purchased the said products in the whole country and patients who may have been administered the products are advised to take a hepatitis test.

Column

Notification for Hepatitis Virus Examination and Hepatitis Treatment

~early detection and early treatment for hepatitis~

Hepatitis is “the condition that the liver has inflammation”.

Hepatitis virus B and C have a high possibility to remain in your liver and cause chronic hepatitis, and may develop cirrhosis/liver cancer.

The number of infected patients with hepatitis virus B and C (hereafter hepatitis virus) are estimated over 3 million in total, and hepatitis is so “familiar” disease that it is said as the largest-scale chronic infectious disease in Japan.

Once developing hepatitis, liver function is gradually deteriorated. However, subjective symptoms are hardly appeared and it has already reached to the serious stage when the patient starts feeling “languid”.

Yet, it can be prevented to develop cirrhosis or liver cancer or the aggravation can be slowed with appropriate health management and treatment.

Therefore, even if you do not have subjective symptoms, it is very important to take a hepatitis virus test once in your life to detect it as soon as possible, and to go to an appropriate medical institute.

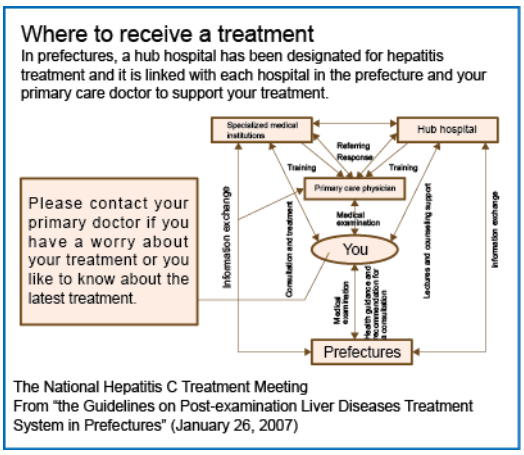
You can have a hepatitis virus test for free in the health centers and the entrusted medical institutes in 136 municipalities (prefectures, cities with a health center and special wards) (Researched in June 2009).

Since the test requires only blood sampling, so it does not take long. If you have never had such the test before, please take it (please contact the municipal office or the health center which your residence belong to for information on the available time and date).

Liver conditions are varied depending on each person and there are cases that symptoms

may never appear even if you are infected with hepatitis virus. Therefore, it is essential to visit a medical institution if infection is confirmed by a test to consult whether or not you need to take a treatment regardless of that subjective symptoms are not appeared yet.

If you are diagnosed hepatitis which needs to be treated, the current effective medical treatments are by interferon for hepatitis B and C, and by the Nucleoside and Nucleotide Analogues for hepatitis B.



The Ministry of Health, Labour and Welfare has been implementing a medical subsidy for interferon therapy since FY2008 so as for as many patients as possible to be able to take appropriate and early treatment without anxiety (prefectures are responsible for implementation and the national government subsidizes them a half of the cost).

Besides, since FY2010 some measures have been taken so that people can make use of the system more easily by extending the medical subsidy system for hepatitis, reducing the burden of patients and adding the treatment by Nucleoside and Nucleotide Analogues to the subsidy.

Subsidy for Medical Expenses of Treatment by Interferon and Nucleoside and

Your monthly medical cost of "treatment of hepatitis C or B by Interferon" and "treatment of hepatitis B by Nucleoside and Nucleotide Analogues" can be reduced depending to your household income.

The following documents are needed. Please contact your prefectural office or the health center near your residence.

①Application for a certificate of hepatitis treatment (treatment by Interferon or Nucleoside and Nucleotide Analogues)
②Medical certificate (Issued by your primary care physician etc.)
③Copy of health insurance card with your name on it (Issued by insurer)
④Copy of a residence certificate on which members of your household are registered
⑤Documents to prove the annual amount of your municipal tax (Issued by the municipal office where you are registered as a resident)

Flow chart after application (Image)

Revised points since FY2010

1. The limit of individual payment has been reduced.
   The limit of individual payment, which was 10,000, 30,000, 50,000 yen before the revision, has been reduced by 10,000 yen (20,000 yen to high income household).

2. Treatment by Nucleoside and Nucleotide Analogues have been added to the subsidy program.
   You can receive subsidy for treatment by Nucleoside and Nucleotide Analogues in addition to the conventional treatment by Interferon.

3. The additional subsidy for the re-treatment by Interferon has begun.
   Patients who received treatment by interferon and proved efficacious can receive the subsidy again for further treatment.

As for treatment by interferon, since strong side effects accompany the treatment, patients mention that it is difficult to receive the treatment due to work and other situation they have to consider about. Therefore, the Ministry of Health, Labour and Welfare is asking patients to share their experiences of interferon therapy, and making leaflets with such experienced in the effort for easing patients' anxiety as much as possible.

I'm here because I made my mind to take the treatment

A few years ago, while I was in hospital due to another disease, I had a blood test and the doctor told me my liver was something wrong. Since then, I took a treatment for three

months but I could not recover from it completely.

After discharge from the hospital, the test value of my liver function was still insecure and I was always worried about it.

In 1997, I was recommended to take interferon therapy by my physician and I had it for a month. However, the result was same as the previous treatment.

Around May 2008, the test value of my liver function started increasing and the doctor told me that my condition was not good enough to respond to interferon and introduced me a specialized hospital, then I resumed taking the treatment. First, I was hospitalized for two weeks. After two weeks, I was introduced to a local medical institution, and I went to the hospital once a month for a year.

I had side effects from the treatment, such as a high fever, a chill, hemorrhage in the eye ground due to retinopathy, and a rash on my upper body, which required a treatment in the dermatologist's. Other than these side effects, I had shortness of breath, taste disorder, numbness on my limbs, loss of hair and mouth ulcer. The doctor told me I had stronger side effects than in usual cases.

Although I almost gave up taking the treatment due to the side effects, my condition is in follow-up stage now because of the negative conversion of the virus.

I'm happy that I made my mind to take that treatment.

Extracted from "About Hepatitis vol.1: My experience of interferon therapy" (possible to download from the website of the Ministry of Health, Labour and Welfare)

http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/siryou.html#poster