Compensation and Insurance for Participants/ Subjects Harmed in Clinical Research Studies:
Process of the Inheritance of Good Clinical Practice (GCP) in Japan and its Present Status

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Tatsuo Kuroyanagi

Attorney-at-Law; Legal Advisor

Japan Medical Association

Revision of the third sentence of paragraph14 of the DoH at Seoul in 2008

- "The protocol should include…provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study."

- Guaranteeing (free) treatment and compensation for loss to subjects who are harmed is at the core of the protection of subjects, and this provision needs to be strengthened further in the future.

Experience of numerous large lawsuits brought by victims of drug-induced suffering against pharmaceutical companies, physicians, and the national government

- Thalidomide
- Streptomycin (SM) hearing loss and shock death
- SMON (subacute myelo-optic neuropathy) caused by chinoform (clioquinol)
- Quadriceps and other muscle contracture resulting from intramuscular injection of chloramphenicol, etc., in infants
- Chloroquine retinopathy

Changes in the Pharmaceutical Affairs Act in Japan, etc.

1960: (New) Pharmaceutical Affairs Act enacted

1961: Universal health insurance coverage launched

1964: WMA DoH adopted

1971: Drug efficacy reevaluation system introduced; sale of Dihydro SM and Compound SM suspended

1975: Revisions to WMA DoH adopted in Tokyo

Changes in the Pharmaceutical Affairs Act in Japan, etc.

1977: Judge Kabe of the Tokyo District Court issued a settlement proposal in the SMON case.

1979: Major revision of the Pharmaceutical Affairs Act; Adverse Drug Reaction Sufferings Relief Fund Law enacted

1989: Good Clinical Practice for Trials on Drugs (Notification) issued by the Director of Pharmaceutical Affairs Bureau, Ministry of Health and Welfare of Japan

1990: Manual of Good Clinical Practice (GCP) for Trials on Drugs published

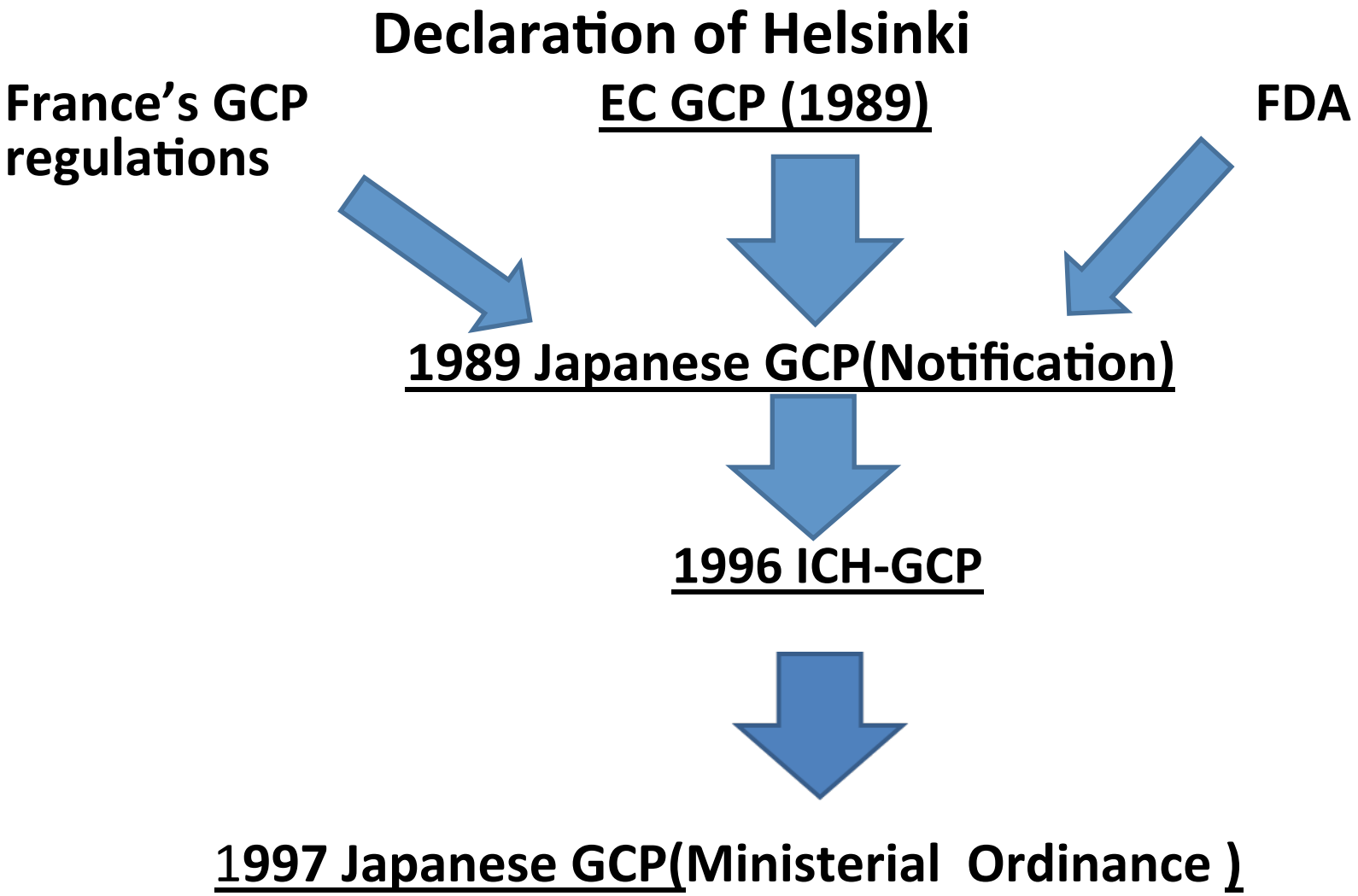
Origin of Japanese GCP

In 1989, the Ministry of Health and Welfare of Japan added the subtitle “GCP” to the Japanese title for the Good Clinical Practice for Trials on Drugs (Notification).

That most likely originated with the EC’s (at the time) Good Clinical Practice for Trials on Medicinal Products in the European Community (1989).

When the above guidelines were announced, the final draft of the EC GCP and the text (in English) of France’s GCP were introduced alongside of the DoH revised at Venice in 1983, FDA regulations (U.S.A.)

Origin of Japanese GCP



Changes in the GCP system (1)
—from administrative guidance to a legal system

1983: Work began on preparing the Japanese GCP

Oct. 1989: Good Clinical Practice for Trials on Drugs (Notification)

Apr. 1990: Manual of Good Clinical Practice (GCP) for Trials on Drugs published

Apr. 1990: Japan, together with the EU and the US, participates in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

Changes in the GCP system (2)
—from administrative guidance to a legal system

Jul. 1995: Product Liability Act went into force

May 1996: ICH-GCP Yokohama Accord

Oct. 1996: DoH Somerset West revision (placebo provisions)

Mar.1997: Japanese Ministerial Ordinance on Good Clinical Practice for Drugs

May1997: About Application of Good Clinical Practice for Drugs

Content of Good Clinical Practice (GCP) for Drugs

1998: Full implementation of new GCP

Inclusion of the GCP system in the Pharmaceutical Affairs Act and establishment of the compensation system for health damage

- 1989 GCP standards when conducting clinical studies (trials) subject to Pharmaceutical Affairs Act, the sponsor was requested (administrative guidance) to take steps to provide compensation and insurance for subjects, and interested parties followed those requests.
- It became essential to insert in consent forms and explanatory statements provisions for “treatment and compensation” in the event a subject’s health is damaged.

Inclusion of the GCP system in the Pharmaceutical Affairs Act and establishment of the compensation system for health damage

- Based on the above provisions, interested parties promised (free) treatment and compensation and, at the same time, requested non-life insurance companies to create indemnity insurance policies that they then took out.
- The GCP ministerial ordinance of 1997 is based on law and the compensation system for health damage was elevated to a legal system. However, it is just a general framework with no definite details spelled out for the compensation system.

Typical example of a “treatment and compensation for health damage” provision

The following is an example of a treatment and compensation for health damage provision:

“Please consult your primary doctor immediately if you develop symptoms during this trial that you did not have before. Appropriate treatment and appropriate measures shall be taken if you suffer an adverse effect or other health damage during or after participation in this trial. You may also receive compensation according to the type and degree of health damage.

However, please be aware that you may not receive compensation if it is found that you did not follow your primary doctor’s instructions or that the health damage was due to your own carelessness.”

Present status of the compensation system

Japan has developed a *compensation* system that covers a victim's loss to a certain limit in exchange for not requiring proof of negligence, with the aim of providing relief for the victim, apart from tort liability that questions negligence and provides *indemnity* for gross damages.

Occupational accidents are one example, which have a compensation system based on the Industrial Accident Compensation Insurance Act. As a rule of thumb, this system determines the amount to be paid (compensation) by removing consolation money from the gross damages items, dividing the degree of harm (loss of capacity to work = after effect) into 14 levels (grades), and taking the grade into consideration, with average wages as the base.

This is the model for many compensation systems (the Automobile Liability Security Act uses the above occupational accident compensation system in certification of after effects impediment).

Present Status of the Compensation System

Even now there is an adverse drug reaction relief system for marketed drugs.

The problem is that, even though the times have changed since the system was developed the system still excludes anticancer and carcinostatic drugs from coverage and discards victims with grade 7 or below injuries for occupational accidents (traffic accidents).

Present status of the compensation system

Two compensation systems

Trials in which healthy individual participate (Phase I):

A system that handles compensation according to the occupational accident compensation system was established by the later period of the old GCP age and has lasted up to the present.

Trials in which patients participate (Phase II and III):

Many pharmaceutical companies proposed to pay in conformity with the compensation system of the adverse drug reaction relief method. The reporter is against this.

Present status of compensation insurance（1）

At present, pharmaceutical companies that conduct trials based on the Pharmaceutical Affairs Act invariably take out liability insurance covering compensation for loss up to the highest amounts of compensation provided by the occupational accident compensation system and the adverse drug reaction relief system, respectively.

This is because they are required to submit the proposed subject consent and information sheet and the certificate of insurance coverage issued by an insurance company to the institutional review board.

Examples of three types of are shown at the next slide.

Present status of compensation insurance（1）

A. Comprehensive Liability Insurance

Certificate of Insurance Coverage

Period: 1st March, 2013～1st March, 2014

Covered Perils Comprehensive General Liability

1)～, 2) Products, 3) Fire Legal, ～6)

Clinical Testing Liability and Experimental Testing of New Drugs Endorsement/Compensation in Clinical Trials Endorsement (The Indemnity provided by this policy shall apply to legal liability and compensation for bodily injury to third parties in clinical trials conducted by or on behalf of the Insured .)

Limit of Liability;～

Present status of compensation insurance（2）

B. Healthy Subject Compensation Insurance

Certificate of Product Liability Insurance Coverage (Schedule)

Insured: ABC Co., Ltd.

Term: Midnight on 1st April 2013 to Midnight on 31st March 2014

Amount payable: Bodily injury liability per person: 100 million yen; per accident: 300 million yen(3.2 million USD)*; during the insurance term: 300 million yen

Deductible: Per accident: 500,000 yen(5,263 USD)

Notes: Clinical Trial Liability Insurance Rider

- Per accident, during insurance term: 300 million yen (coverage for bodily Injury liability per accident, payment within the limit during the insurance term)
- Coverage limit per victim: as shown on reverse (no exemption from responsibility)

25th February 2013

〇〇〇 Fire Insurance Company

*US dollar/JPY exchange rate: US$1 ≒95 yen

Present status of compensation insurance（3）

B. Reverse

Coverage limit per subject

Degree of health damage: trial on healthy individuals

Payment limit (per subject)

Death: 30 million yen(0.3 million USD)

After effects impediment grade 1: 90 million yen (0.9 million USD)

After effects impediment grade 2: 90 million yen (0.9 million USD)

After effects impediment grade 3: 70 million yen (0.7 million USD)

After effects impediment grade 4: 65 million yen (0.7 million USD)

After effects impediment grade 5: 55 million yen (0.6 million USD)

After effects impediment grade 6: 50 million yen (0.5 million USD)

After effects impediment grade 7: 40 million yen (0.4 million USD)

After effects impediment grade 8: 32 million yen (0.3 million USD)

After effects impediment grade 9: 25 million yen (0.3 million USD)

After effects impediment grade 10: 20 million yen (0.2 million USD)

After effects impediment grade 11: 15 million yen (0.2 million USD)

After effects impediment grade 12: 10 million yen (0.1 million USD)

After effects impediment grade 13: 7 million yen (0.1 million USD)

After effects impediment grade 14: 4 million yen (42,105 USD)

Lost work time compensation payment: 13,000 yen (137 USD) per subject per day for the period beginning on the fourth day of no wages due to lost work time

Present status of compensation insurance（4）

C. Patient Subject Compensation Insurance

Certificate of Product Liability Insurance Coverage

Policy Owner: XYZ Co., Ltd.

Insured: XYZ Co., Ltd.

Term: Midnight on 1st January 2013 to Midnight on 31st December 2015

Coverage limit: Bodily injury liability per person: 100 million yen (1.1 million USD) ;
per accident: 500 million yen (5.3 million USD);
during the insurance term: 500 million yen

Deductible: Bodily injury liability per accident: 1 million yen (10,526 USD)

Notes: Investigational drug code: PP-001; investigation drug rider ancillary;
clinical trial compensation
liability insurance ride ancillary
Death: 20 million yen (0.2 million USD)
After effects impediment grade 1: 70 million yen (0.7 million USD)
After effects impediment grade 2: 50 million yen (0.5 million USD)

25th November 2012

ZZZ Marine Insurance Company

Reporter note:

Since after effects impediment grades 1 and 2 are the only ones covered by the insurance, it is clear that only compensation equivalent to the adverse drug reaction compensation system is being considered.

Compensation for clinical research besides trials "Ethical Guidelines on Clinical Research" (1)

- ICH-GCP (6) does not distinguish between clinical trial studies subject to the Pharmaceutical Affairs Act and other clinical research. The government requires interested parties to comply with the GCP ministerial ordinance of 1997, limited to studies subject to the Pharmaceutical Affairs Act, but it has done nothing to develop standards relating to clinical research not covered by the Pharmaceutical Affairs Act.

- On July 30, 2003, the Japanese Ministry of Health and Welfare established Ethical Guidelines on Clinical Research, but they are nothing more than administrative measures. These guidelines went through a major revision of DOH in 2008 and have come down to the present.

Compensation for clinical research besides trials "Ethical Guidelines on Clinical Research" (1)

- Statements regarding compensation for subjects were apparently strengthened during the 2008 revision. The heads, etc., of clinical research organizations are required to "take out insurance and take other necessary measures for compensation for health damage to subjects," and to "sufficiently explain beforehand the content of insurance and other necessary measures for compensation for health damage and obtain subjects' consent."

Compensation for clinical research besides trials "Ethical Guidelines on Clinical Research" (2)

- However, with the provision that, "**the existence or non-existence of compensation for health damage** to subjects associated with the conduct of the clinical research must be indicated in the clinical research protocol," if it is indicated that compensation will not be provided and the subjects' consent is obtained, compensation is not needed. Further, by expressing the view that, "Other necessary measures refers to things such as the provision of medical care for health damage or the provision of other services," it pulls down with its own hands the foundation of the basic principles built at the beginning.

Compensation for clinical research besides trials (present status – 1)

- Research besides clinical research subject to the Pharmaceutical Affairs Act is mainly conducted by university hospitals and national, public, or other large medical institutions. In recent years, a variety of clinical research has been conducted jointly by multiple institutions (and sometimes even with institutions in other countries).

Compensation for clinical research besides trials (present status – 1)

- Restricting our conversation to research in Japan, the biggest financer or aid provider for research funding for these studies is most likely the national government. The problem is that aid is not always sufficient, and researchers are forced to conduct research with minimal outlays. As a result, the reality is that even if there is a need, they cannot take out insurance to cover compensation.
- This results in a situation where clinical research —despite being cutting-edge research—continues unreservedly without compensation.

Compensation for clinical research besides trials (present status – 2)

The following is an example use by an organization called JCOG.

"There is a possibility of developing unforeseen serious complications or other health damage during or after completion of participation in this clinical study. In that case, appropriate responses will be taken, the same as with treatment for health damage in usual medical care. However, the medical expenses shall be borne by the patient, since the treatment will be provided as health-care services provided under health insurance, the same as usual treatment.

If you feel some kind of health damage that does not occur during usual treatment, as a result of participation in this clinical study, inform your doctor without reservation. Also note that no sympathy money, other type of benefit, or any kind of special financial compensation has been prepared for health damage sustain in this clinical study."

Reporter note:

JOCG (Japan Clinical Oncology Group) is a research organization run partially with research funding of an Oncology Grant-in-Aid from the Ministry of Health, Labour and Welfare and partially with a Health and Labour Sciences Research Grant called a Grant for the Third-Term Comprehensive 10-Year Strategy for Cancer Control. It consists of 13 specialty study groups and enjoys the participation of nearly 200 hospitals across Japan.

Compensation and insurance for clinical research besides trials

- A lot of clinical research not covered by the Pharmaceutical Affairs Act is conducted in many education-related hospitals such as university hospitals, and recently regulatory agencies have started to provide strong direction to take out compensation insurance.
- As a result, researchers are hoping to take out insurance, but with little understanding on the part of interested parties, the reality is that there is not even a form in place, as compared to trials that have only just gotten underway.
- The legislation of guidelines with solid content needs to take place as soon as possible, the same as with pharmaceuticals, in order to realize the principles of the ICH-GCP, which aimed for substantial championship of subjects. This is an urgent issue to be resolved that has been left before us.

Conclusion

- I attempted to put the current status of today's issues in Japan into a figure to wrap up today's report.

Conclusion

	GCP ministerial ordinance		Ethical guidelines on clinical research
Subject to	Clinical studies (trials) covered by the Pharmaceutical Affairs Act		Other clinical studies
Subjects	Health individuals	Patients	Health individuals/ patients
Compensation	Yes	Yes	Provision exists, but "without compensation" accepted
Content/ degree	Similar to the occupational accident relief system (grade 1 to grade 14)	Similar to the adverse drug reaction relief system (excludes grades 8 and below from the occupational accident system and anticancer drugs)	Actual condition is chaotic
Backed up by insurance	Yes	Yes	Insufficient/ undeveloped
Type of insurance	• Treatment only	• Treatment only	
	• Combined with product liability insurance, etc.	• Combined with product liability insurance, etc.