Conflicts of Interest in Drug Evaluation

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1. Close ties between industry, government and academia in Japan

(1) Medwatcher Japan (official Japanese name: “Yakugai Ombudsperson”) was launched on June 8, 1997, the year after the legal settlement for the tainted blood products-induced HIV litigation, at the urging of the plaintiffs lawyers group of the HIV litigation. A key phrase associated with the HIV tainted blood scandal is “corrupted relationship” (Japanese: “yuchaku”). It had been mentioned frequently that “government bureaucrats getting consulting jobs with private companies” and “economic ties between leading experts and pharmaceutical companies” had been creating a hotbed for repeated drug-induced disasters.

(2) However, on the other hand, national policy trends aimed at these close ties between industry, government, and academia had already started at that time. For example, the “University Technology Transfer Promotion Law” (1997) and the “Industrial Revitalization Law” (1999), with a Japanese version of Bayh-Dole provisions, have been enacted. It is said that this trend had been almost 2 decades behind the U.S. Likewise, the issue of conflict of interest has been taken up in Japan 2 decades behind the U.S.

2. Cases in Japan dealing with “conflict of interest” issues

(1) Well-known cases revealing “conflicts of interest” include the cases of the clinical trial investigators receiving pre-marketed stocks (2004), conflicts of interest with Japan Lung Cancer Society guideline committee members concerning gefitinib, which has caused numerous drug-related deaths (2005), and large contributions by the pharmaceutical company selling Tamiflu to a chief researcher of a Ministry of Health, Labor, and Welfare (MHLW) study group on influenza (2006).

(2) Medwatcher Japan has raised questions, published comments and appealed for regulations in connection with these conflicts of interest, but we had to wait until the Tamiflu incident to realize the official policy by the MHLW.

3. Research

(1) Issues and regulations concerning “conflict of interest” are being explored from 3 broad perspectives: general research; creation of guidelines; and drug approval review and post-marketing safety management.

The first area is general research. The MHLW and Ministry of Education, Culture, Sports, Science, and Technology have published various regulatory policies and

guidelines, including a Conflict of Interest Working Group report (2002) and conflict of interest policy guidelines for clinical trials (2006), but the content is not explicit and specification of the above regulatory policies has been left to each university's decision.

As of 2007, only 22 of 79 university medical schools in Japan had adopted their conflicts of interest rules. It is not even confirmed whether or not the remaining universities have such rules.

(2) In response to conflict of interest problems with Tamiflu, the MHLW, on March 31 of this year, finally issued a conflict of interest management guideline (Notification No. 0031001 from the Director General, Health Sciences Division, MHLW, March 31, 2008).

The guideline requires establishment of regulations and committees at major universities to manage conflicts of interest and reviews by committees at each university before applications are made for grants and subsidies. The guidelines apply to scientific research supported by MHLW grants, and if these guidelines are not followed, investigators at each university are unable to receive MHLW research grants. This has prompted universities to adopt regulations. However, a problem with the guidelines is that specific regulations are left to the discretion of each university,

4. Treatment guidelines

(1) The second area is treatment guidelines. Most of these guidelines are established by academic societies and MHLW working groups, which have a great deal of influence on drug treatment in clinical practice. This creates a serious potential for negative effects caused by "conflict of interest".

(2) However, as of 2007, only the Japanese Society of Clinical Oncology and Japanese Society of Medical Oncology had established regulations on conflicts of interest. Among 68 major disease guidelines, financial support by treatment manufacturers to physicians preparing the guidelines was disclosed in only 3 cases. The enactment of regulations is long overdue.

5. Drug approval review and safety management

(1) Drug approval review and safety management system in Japan

The third area is drug approval review and safety management. This area requires the most strict regulations to eliminate abuse in conflict of interest situations.

In Japan, the drug approval system is administered by the Pharmaceuticals and Medical Devices Agency (PMDA). Reports are compiled and then reviewed by an MHLW council comprised of outside experts and approved by the MHLW Minister. Drug safety is also reviewed by MHLW expert groups based on information gathered by the PMDA. Let us examine each of these systems.

(2) PMDA

The PMDA is an independent administrative organization in charge of drug review that was started in 2002.

It was initially planed to hire pharmaceutical personnel widely, but after objections by drug-related victims, Medwatcher Japan, TIP and JIP campaigns, regulations to restrict the employment of pharmaceutical company personnel were established.

However, in 2007, the report of "the MHLW advisory board for accelerated approval of effective and safe drugs" mentioned that it should partially deregulate the employment regulation. This is obviously problematic.

Enactment of regulations to prevent conflicts of interest among staff members and conflicts of interest among 934 outside expert members (as of February 2008), is thus an urgent priority.

(3) Pharmaceutical council and advisory board

To prevent conflicts of interest among pharmaceutical council and advisory board members, regulations were established after the Tamiflu incident. In late March of this year, "rules for committee participation" were established.

Key points of these regulations are as follows: <1> Clinical trial staff, company consultants, and patent holders of the drug being reviewed, regardless of compensation received, cannot participate as committee members; <2> Persons receiving more than 5 million yen from an individual company cannot participate in the discussions. If the amount is between 500,000 and 5 million yen, that person can participate in discussions, but not in final decisions; <3> Self declarations regarding conflict of interest are made for the preceding 3-year period and disclosed on a web site; <4> A committee is set up to continually review the status of conflict of interest regulating system.

These regulations reflect many comments and opinions by Medwatcher Japan. However, still many problems remain, the required content of the disclosure is vague and the monetary upper limit of regulations is not yet sufficient to regulate the conflict of interest.

6. Prevention of drug-induced disasters and conflicts of interest

In conclusion, let us examine "conflict of interest" issues from the perspective how to prevent drug-induced disasters:

(1) We must address to the fundamental question of whether the promotion of "industry, government and academic collaboration" as a national policy actually benefits patients.

(2) We must take advantage of our position as a "latecomer" in the conflicts of interest field. We need to carefully listen to those indicating the limitations of FDA and EMEA regulations and learn from the US and EU experiences. A "keeping-up-with" FDA or EMEA approach is not always a good idea.

(3) Regulation of "conflict of interest" requires absolute disclosure of all financial

connections. However, we must also realize that this is “not a cure-all”. Fact-finding surveys and constant vigilance by citizens groups are essential to continually revising existing regulations.

(4) A comprehensive system must be designed to resolve the issue of conflicts of interest. Public disclosure of all clinical trial and non-clinical trial data, adverse reaction information, protocols, and requirements for clinical trial registration (including phase I studies and protocols) and establishment of publicly funded clinical trials system are essential. In Japan, even the laws of patients’ rights and the act for the protection of human research participants’ clinical trial have not been formally enacted. Solving “conflicts of interest” requires international cooperation. We sincerely hope that this 10th anniversary symposium of Medwatcher Japan will provide an opportunity to open new doors to address together to the issue of “conflict of interest”.