Conflicts of interest in Japan

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Lessons from the HIV-tainted-blood Scandal: Government-Industrial-Academic Complex

- The launch of Medwatcher Japan(1997)
- The legal settlement for the HIV litigation(1996)
- "Corrupted relationship": the keyword of the scandal
  - -government bureaucrats getting consulting jobs with private companies
  - -economic ties between leading experts and pharmaceutical companies
- Deals by MHLW
  - -separation between regulatory and promotion
  - -ban of golden parachute

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Acceleration of close ties between industry, government and academia

- University Technology Transfer Promotion law(1998)
- Industrial Revitalization Law(1999)
  Japanese version of Bayh-Dole provisions(Article300)
- Industrial Technology Enhancement Act(2000)
- Promoting 1,000 venture enterprises from University Campus: 3-Year-Plan (2001)

※ Japan is 2-decades-behind in Business-Academia Collaboration, compared to the U.S.
(Bayh-Dole Act in the US, 1980)

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Three well-known cases

- The clinical trial investigators receiving pre-listed shares of stock in Osaka University (2004)
- Guideline-Committee members of Japan Lung Cancer Society had sustained strong links with AstraZeneka cencerning gefitinib (2005)
- Large contributions by pharmaceutical company selling Tamiflu to the chief researcher of MHLW study group of influenza(2006)

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Gefitinib(iressa)

- Drug for lung cancer (AstraZeneka)
- First approval in the world (July 5th, 2002)
- Advertisements: less toxic "molecular target drug" "dream new drug"
- Doctor letter(Oct. 2002)
  - -26 interstitial pneumonia including 13 deaths
- 1796 interstitial pneumonia including 709 deaths (as of Mar.2007)
- No survival advantage in the phase **III** trials
  → withdrew the application in EU (Jan. 2005), prohibited administration for new patients in the US (Jun. 2005)

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Japan Lung Cancer Society committee members for drafting "guideline concerning gefitinib use"

- Conclusion of the panel on gefitinib in MHLW
  →allow continuing use of gefitinib based on Japan Lung Cancer Society guideline (Mar. 2005)
- Among 10 members:

At least 5 members are involved in clinical trials
At least 3 members are involved in the articles offered by AstraZeneka

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Subjects of Survey

- General research
  university・research institution
- Creation of guidelines
  academic conference etc.
- Drug approval review, post-marketing safety management
  committees and panels in MHLW
  PMDA (**Pharmaceutical Medical Devices Agency**)

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Guidelines issued by MHLW & MEXT and the regulations in each university

- Conflict of Interest Working Group report (2002)
- Ethical guidelines for epidemiology studies (2002)
- Ethical guidelines for clinical studies (2002)
- Conflict of interest policy guidelines for clinical studies (2006)

→

- Adopting regulations in each university and research institution
- Only 22 of 79 university medical schools in Japan had adopted regulations concerning COI
  (The Mainichi Newspapers, Mar.2008)

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COI management guideline on Researches subsidized by MHLW

- Grants for Health Science-researches by MHLW subsidies
- The Tamiflu scandal forced MHLW to form a board to make COI management guideline on scientific researches subsidized by MHLW in May, 2007
- A COI management guideline issued in Mar.2008

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COI management guideline on Researches subsidized by MHLW - outline

- Reviews by conflicts of interest committees at each university before applications are made for grants and subsidies
- Establishment of regulations and committees at each university
- Reports to MHLW from each university in the event of problems
- Investigational authority of MHLW

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COI management guideline on Researches subsidized by MHLW - criteria

- Rule and judgement are left to each university
- Indication
  -reports about stocks etc.
  -an annual lecture fee of more than 1 million yen from one company
  -research fund of more than 2 million yen from one company
- Problems
  - depends on each university
  - no reliable indication
  (a sample survey in July, 2007)

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Treatment guidelines – attitudes of academic society

- A strong influence on drug treatment in practice
- As of 2007,
  Only the Japanese Society of Clinical Oncology and Japanese Society of Medical Oncology had published "the guideline for conflicts of interest on cancer clinical studies"
- Answer from The Japan Lung Cancer Society to our inquiry (Nov. 2005)
  "As this guideline was established by The Japan Lung Cancer Society itself, we do not think it is necessary to disclose COI concerning each committee member."

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Treatment guideline – current situation of management

- Among 68 major disease guidelines, financial support by pharmaceutical companies to physicians drafting the guidelines was disclosed in only 3 cases.
- In 2 cases, despite huge financial support, it was written that there was no financial support from pharmaceutical companies.

(by the report of the research subsidized by MHLW)

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Drug approval, review and safety management

- Pharmaceuticals and Medical Devices Agency(**PMDA**)-substantial reviews
- Expert committee members
- MHLW councils, investigative commissions, investigation committees etc.

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PMDA (Pharmaceutical Medical Devices Agency)

- **Established in 2002**
- **310 people in approval review division, 66 people in safety management division**
- **Planned**

to unite not only these 2 division but the industrial development division

to widely hire pharmaceutical company personnel

↓

This attempt was changed through active campaigns by Medwatcher Japan, TIP, NPOJIP, and drug-related victims

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PMDA - restriction of employment

- **Employment regulations**

① For 2 years after retirement from PMDA, one cannot be employed with the jobs closely related to those positions in PMDA, 5 years prior to retirement

② For 2 years after employment by PMDA, one cannot be involved in the services closely related to the jobs in the pharmaceutical company, 5 years prior to employment by PMDA

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PMDA – restrictions of employment

- The report by "the MHLW advisory board for accelerated approval of effective and safe drugs" (2007)

refers to partially deregulated the employment regulations

- a request for the source of manpower

"Medicines Control Agency" plan

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PMDA –advisory experts

- Regulation of COI for advisory experts
  As of Feb. 2008, 934 experts
  Regulation with reference to MHLW boards
  Who and how involved in What
  Even the names of all members are not disclosed
- The other regulations of COI
  (except the employment regulation)

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Regulation System for New Drug Approval and Pharmacovigillance

- MHLW has various advisory boards and regulatory meetings on drug approval and pharmacovigillance
- MHLW started to review COI because of the Tamiflu scandal in May 2007
- Compliance Requirements for the members of the advisory committee (Mar. 2008)

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"Compliance Requirement for advisory committee" - outline

- Clinical trial researchers, company consultants, and patent holders of the drug being reviewed are excluded from the discussion and vote of the board, regardless of the amount of money
- Receiving amount–from an individual company
  ≧5,000,000 yen/Year : excluded from discussion
  ≧500,000 yen/Year : excluded from vote
- COI must be declared for the past 3 years
- Self declarations are put up on the web site (however, amount of money is not specified)
- Required content of disclosure is vague

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"Compliance Requirement for advisory committee" - problems

- The upper limit of money to exclude committee participation
  -based on individual company
  -too high upper an limit
- The method of disclosure of information
- How to discuss exceptional cases

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Fundamental Questions

- The explanation "the regulation insofar as not to disturb business-academia collaboration"
- The discussion about the treatment of "scholarship donations"
- The effects of disclosure rules
  - thorough disclosure is essential but not enough
- Discussion without fact-finding survey

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Prevention of drug-induced disasters and COI

- Fundamental questions of the "Government-Industrial-Academic collaboration"
- Critical analysis of current conditions in EU and US to learn lessons from their experiences
- Survey and constant vigilance by citizen groups
- Multiple and multilayered institutional design
  -clinical trial registration
  (including phase Ⅰ and protocols)
  -public disclosure of all clinical trials
  -publicly funded clinical trials system
  -overhaul of the pharmacoregulatory system
- **International cooperation**

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