The Selling Sickness Conference, Amsterdam, 7-8 October 2010

Distorted Drug Evaluation:
IRESSA and Conflicts of Interest among Experts in Japan

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Backgrounds

(1) Repeated drug-induced disasters in Japan

Year	Drugs	Adverse reactions
1962	Thalidomide	Phocomelia
1970	Clioquinol（Chinoform）	SMON: subacute myelo-optico-neuropathy
1970	Coralgil	Liver disease
1974	Chloroquine	Retinopathy
1984～92	HIV tainted unheated coagulation factor preparations	AIDS
1987～94	HCV tainted fibrinogen preparations	Hepatitis C
1993	Sorivudine and 5-FU	Augmentation of activity of 5-FU
2002～10	Gefitinib（IRESSA）	Interstitial Lung Disease (ILD)

(2) Medwatcher Japan

- A non-profit organization including 17 members: 7 pharmacists, 5 attorneys, 1 physician, 1 consumer advocates, 1 thalidomide victim, 1 sociology professor and 1 medical journalism professor
- Launched in 1997, the year after the legal settlement for the tainted blood products-induced HIV litigation
- Objectives: to monitor and prevent drug-induced disasters
- Activities
  - To submit appeals, public questions and comments to governmental agencies and pharmaceutical companies regarding issues related to individual drugs
  - Law suits based on the freedom-of-information act
  - Nation wide surveys
  - Symposia
  - Lobbying activities
- Cooperating with “The Informed Prescriber” (TIP) and “Non Profit Organization Japan Institute of Pharmacovigilance” (NPOJIP)

(3) Drug-induced accidents due to IRESSA

- IRESSA
  - An orally administered drug, gefitinib for non-small cell lung cancer
  - An epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor
  - Globally first launched by AstraZeneca in Japan

- IRESSA victims

* No. of deaths before approval: 34

Date	No. of deaths from ILD (After approved Jul. 5, 2002; accumulated *)
Jul. 15, 2002	1(First report of fatality)
Dec. 31, 2002	180
Dec. 31, 2004	557
Dec. 31, 2009	799
Mar. 31, 2010	810

Objectives

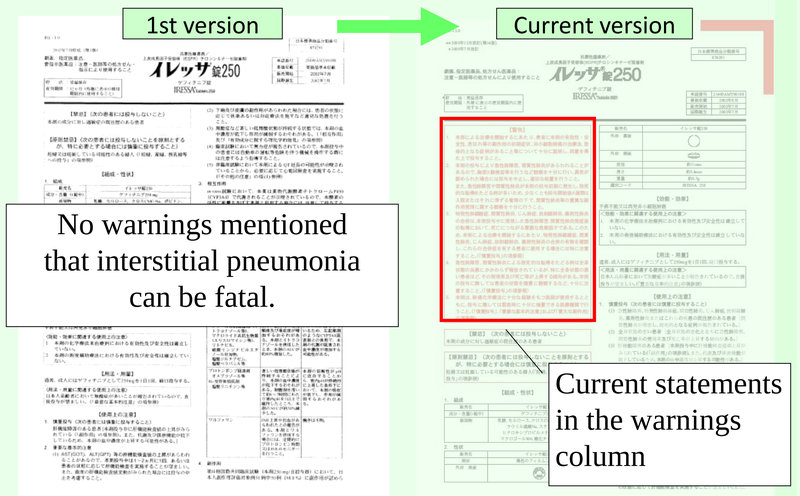
- **To describe the conflicts of interest involving experts, promotional advertising by pharmaceutical companies and IRESSA drug information, and examine solutions to those issues.**

Methods

- **We reviewed the facts regarding conflicts of interest involving experts clarified through the IRESSA litigation and a promotional advertising disguising itself as ‘scientific drug information’. We also examined the characteristics of IRESSA drug information provided by the pharmaceutical company.**

(2) Inadequate warning statements

IRESSA package insert

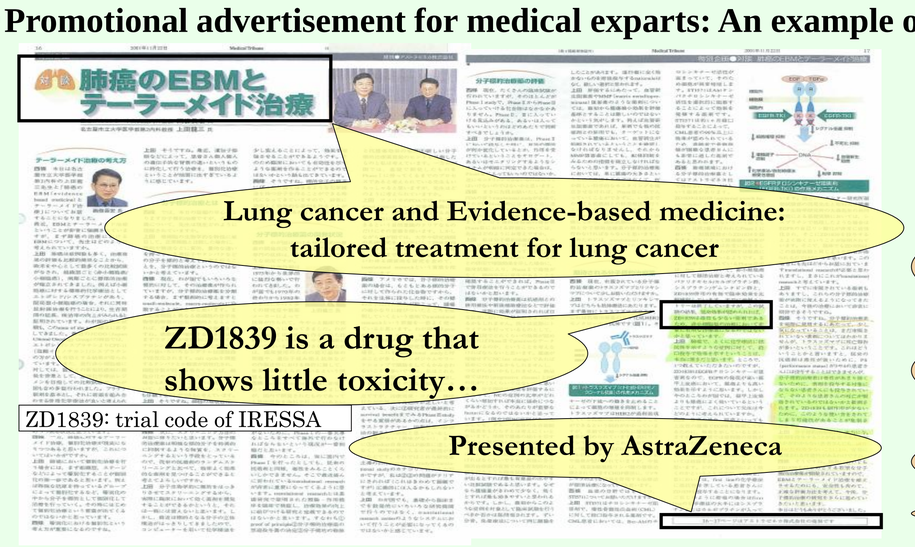


Findings

(1) Promotional advertisement masquerading as science: IRESSA’s case

Characteristics of Contents	Methods of advertising
・Emphasis on efficacy	・Directed at all parties (doctors, patients, mass media)
・Emphasize that there are few adverse reactions	・Advertisement masquerading as providing of scientific information
・No mention of interstitial pneumonia	・Predating approval

・Promotional advertisement for medical exparts: An example of IRESSA



・Advertisement implying that the drug has a drastic effect and no serious adverse effects: some examples of phrases in IRESSA drug information

- “The best promising molecular targeted drug for solid carcinoma”
- “An epoch-making drug in the treatment of lung cancer”
- “A wonder and dreamlike medicine”
- ……

(3) Conflicts of interest among 10 expart members of the IRESSA guidelines committee

No.	Name	Defense witness	Member of WJOG**	Investigator of Clinical Trials of IRESSA
1	N. Saijo	✓		✓
2	M. Fukuoka	✓	✓	✓
3	S. Negoro		✓	✓
4	S. Kudo	✓		✓
5	T. Tamura			✓
6	H. Tada		✓	✓
7	T. Mitsudomi	✓	✓	✓
8	H. Kato		✓	
9	N. Yamamoto		✓	
10	K. Hayakawa			

** West Japan Oncology group (Twenty million yen per year was donated to the WJOG from AstraZeneca. The total amount of the donation reaches about 100 million yen.

Discussions

- Ambiguous legal definition of advertisement for pharmaceuticals
- Lack of authorised appropriate medical information for patients.
- A hotbed of drug-induced disasters
  - Insufficient transparency of MHLW advisory committee and guidelines committee, etc.
  - “Corrupted relationship” between pharmaceutical industries and the government.
  - Economic ties between leading medical experts or patient support organization and drug companies

Conclusions

(1) Promotional advertising and DTCA
- Promote the distribution of authorised appropriate drug information to protect the public from misleading information provided as DTCA.
- Review the definition of the advertisement to regulate advertisement masquerading as the scientific information.
- Research the potential impact of the marketing strategy upon the activities of self-help patient group, and reveal the problems relating to the economic ties between patient support organization and drug companies.

(2) Inadequate warning statements
- Set up the committee including patient representatives to check the contents of package inserts. The committee should be held ahead of the approval of drugs, being opened to the public.

(3) Conflicts of interest among experts
- Promote the education of the medical students about issues concerning the relationship between physicians and commercial enterprises.