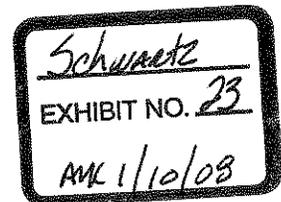


Labeling Change in Japan

Labeling change process and Proposal for the future

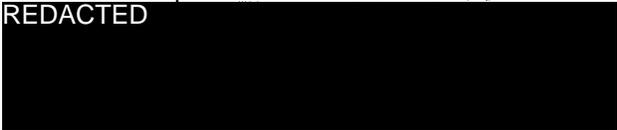
K.Oshitani
Postmarketing Surveillance
Fujisawa Pharmaceutical Co.,Ltd.



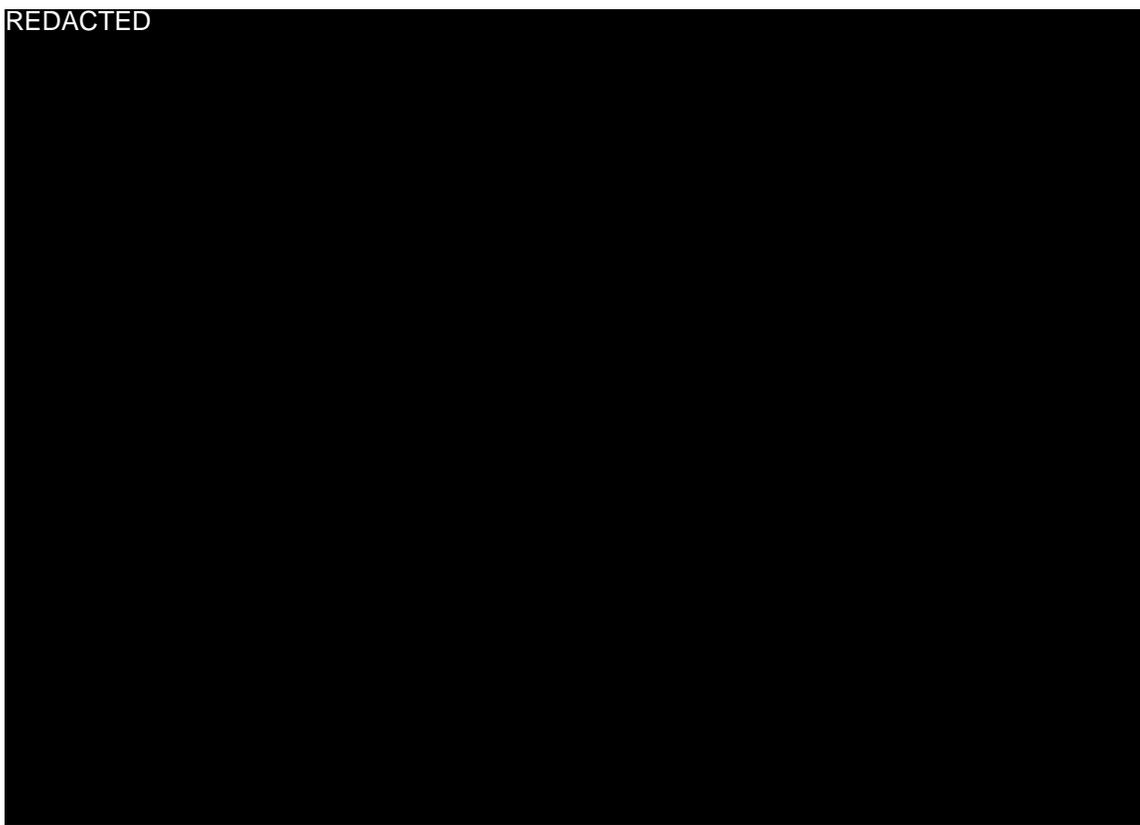
Purpose of this presentation

- Labeling change process in Japan
- Proposal
 - ◆ Seroquel Diabetes case
 - ◆ Seroquel Convulsion case

REDACTED



REDACTED



Fujisawa: decision making process -step 1

- Fujisawa SOP on examining any measure steps
 - a) Timing of report on the adverse reactions and infections, which require special attentions.

Unexpected*		Expected, Serious
Serious	Not serious	
When the 3 rd domestic case is reported	When the 10 th domestic case is reported	When many, normally ten domestic cases are reported or when the 3 rd death case is reported

* Unexpected : adverse reactions that are not expected from 'Precautions'

- b) When remarkable changes of frequency and condition in adverse reaction and infection incidence occur, some measure steps should be examined.

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Fujisawa: decision making process -step 2

- PMS* *Taisaku-kaigi*,
special committee for coping with the situation
 - ◆ The committee makes a decision for the measure steps (e.g. drug proper use including labeling change).
 - ◆ The result turns out to be the final decision by PMS supervisor.

* PMS : Post Marketing Surveillance

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MHLW: decision making process

- Examine at *Jimu-kyoku* review meeting
 - ◆ The relevant specialists take part in *Jimu-kyoku* review meeting.
 - ◆ Labeling change is discussed.
 - ◆ The meetings were held ten times from April to March in 2002.
 - ◆ If necessary, they listen to the advice of Committee on Safety of Drugs, and then make the final decision.

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MHLW: Direction to companies

- Timing

After about 3 weeks from Jimu-kyoku review meeting.

- Variation

- 1 . lyakuan-shiji, notice from the section chief of Safety division Pharmaceutical and food safety bureau MHLW
- 2 . Jimu-renraku, notification at the official level
- 3 . Jishu-kaitei, voluntary change on company's own judgement

Dear Doctor Letter

- Most urgent MHLW direction order
 - ◆ 'Dear Dr. Letter' is *iyakuan-shiji* matter
 - ◆ This is directed when MHLW judged it as very important for safety, and needed to be informed to doctors immediately.
 - ◆ Contents of the labeling, also the contents of 'Dear Dr. Letter' itself and its distribution schedules are strictly regulated by MHLW.
- Demerit when a company receives it
 - ◆ Urgent matter
 - ✦ burdensome task
 - ✦ no room for consideration
 - ◆ Negative impact on the market

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Seroquel Diabetes case

REDACTED

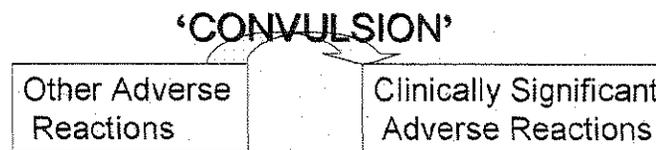


- Scientific examination has not been done enough.
- We don't want to repeat the same mistake.

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Seroquel Convulsion case Fujisawa's Proposal

- A transposition of the precaution statement regarding convulsion from the 'Other Adverse Reactions' section to the 'Clinically Significant Adverse Reactions' section at the time of the revision of the Seroquel package insert accompanied with the license transfer is recommended.



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Seroquel Convulsion case Proposed Statement

- Clinically Significant Adverse Reactions
 - ◆ Hyperglycemia (*omission*)
 - ◆ Syndrome malin (*omission*)
 - ◆ Convulsion (incidence unknown) may occur. If any of such symptoms occurs, this product should be discontinued and appropriate measures should be taken.
 - ◆ Tardive dyskinesia (*omission*)

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Seroquel Convulsion case Japanese Case Reports

- 20 cases of convulsion were reported in Japan.
- Status epilepticus occurred in 4 of them and a life-threatening generalized epilepsy in another case.
- Causal relationships to Seroquel can not be completely ruled-out in these 5 cases although other causes may be considered more suspect.

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Seroquel Convulsion case

Incidences of Convulsion in P3/P4 Clinical Trials in Japan

	Pre-approval	Post-approval
■ Seroquel	0.68% (4/584)	
■ Zotepine	1.86% (16/861)	1.95% (101/5176)
■ Pimozide	0% (0/521)	0.04% (1/2311)
■ Sulpiride	0.10% (2/1906)	0.01% (2/15104)
■ Olanzapine	0.17% (1/580)	
■ Perospirone	0% (0/429)	

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Seroquel Convulsion case

Consistency with other Antipsychotics Package Inserts

- 'Convulsion' is listed in the 'Clinically Significant Adverse Reactions' section in all of the package inserts of other antipsychotics such as zotepine, pimozide and sulpiride that Fujisawa is selling.
- The potency of Seroquel lowering the seizure threshold is considered lower than zotepine but equal to or higher than pimozide and sulpiride.

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MHLW Stance

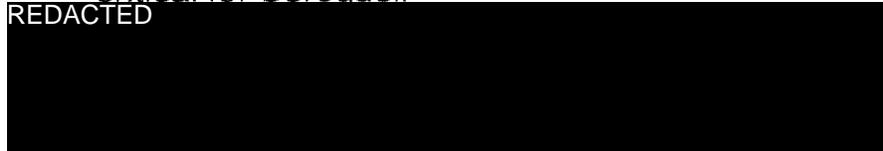
- Punish those who are suspicious!
 - ◆ Certainly, there is insufficient evidence to warrant a change regarding seizures in the Seroquel package insert at this time.
 - ◆ Conversely, we might have to think that there is no evidence to guarantee that the change is unnecessary.

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The Best Way for AZ and Fujisawa

- Seroquel is very efficacious for patients with its proper use.
- We presume next 'Dear Dr. Letter' would be critical for Seroquel.

REDACTED



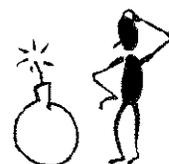
- Please understand the local situation and agree with label changes even if it is not on CDS.

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The Best Way for AZ and Fujisawa

Prevention is better than cure

No more 'Dear Dr. Letters' !



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