

Session 1. Report 2.

ICH TOPIC "6 vs 12 MONTHS"
FOR LONG-TERM REPEATED DOSE STUDIES IN DOGS

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This is a progress report of ICH Topic "6 vs 12 months" for the long-term repeated dose toxicity studies in dogs. Regarding the duration of the long-term repeated-dose toxicity studies, three regions (Japan, the EU and USA) concurred with the 6-month period for rodents, but failed to reach a consensus about non-rodent studies in the ICH 1 in Brussels, 1991. The progress of ICH activity on this topic after the ICH 1 was as follows :

- 1) ICH 1 in Brussels, November 1991
"Six month studies would generally be acceptable, although the FDA indicated that an exception would be made in certain circumstances which justified the need for a 12 month study." was confirmed among 3 regions.
- 2) EWG Meeting in London, July 1992
The JPMA, CMR (Centre for Medicines Research) and FDA introduced their own databases^{1), 2), 3), 4)}. Though Japan and EC recommended the six-month duration according to these reviews, the FDA insisted that the adoption of the six-month was still premature.
- 3) EWG Meeting in Brussels, March 1993
The FDA proposed a prospective research.
- 4) EWG Meeting in Washington, July 1993
Japan and EC did not promise to actively support the FDA "prospective research"

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proposal.

- 5) ICH 3 in Yokohama, November 1995
The FDA (Dr. DeGeorge) proposed a 9 month study based on the re-analysis of 18 cases of databases of the JPMA, CMR and FDA⁵⁾.

The JPMA and CMR surveyed retrospectively their databases, and concluded that almost all compounds did not produce new and toxicologically significant findings after 6 months (Table 1). The results were presented in the ICH EWG meeting in London, July 1992, and published in a journal¹⁻²⁾. In addition, the JPMA and CMR performed questionnaires against the pharmaceutical companies, and obtained similar results^{2), 6)} (Table 2).

In accordance to ICH 1 recommendation, the MHW revised the previous guideline for toxicology studies (issued in 1989)⁷⁾, and changed the dosing duration of long-term toxicity study in non-rodents from a 12-month to a 6-month in the present guideline (issued in 1993)⁸⁾, on the condition of "a 12-month study should be considered in a certain case". The additional notice for the guideline, KAISETSUSYO⁹⁾ states that there is a possibility that the dosing duration would be revised depending on the progress of the ICH.

The proposal of a 9 month period by Dr. J. DeGeorge¹⁾ of the FDA was based on reviews of 18 cases (7 FDA, 3 CMR, 5 JPMA, 2 Bayer Corp., 1 Zeneca Corp.) (Tables 1 and 3). At the ICH EWG meeting in Washington, May 1996, the CMR reported the interim results of the questionnaire on the feasibility of a 9-month

Table 1. New Findings after 3 or 6 Month in Dog Long-Term Toxicity Studies ¹⁻⁵⁾.

Database	Dosing period compared	No. of compounds surveyed	New significant findings	No new finding	Extension of short-term study	Toxicologically significant	Exaggerated pharmacological effect
JPMA	3vs12M	90*	0	82	6 (4)	—	2 (1)
FDA	6vs12M	27	5 (5)	14	8	—	—
CMR	6vs12M	42	3 (3)	21	—	18	—
6vs12M							
Bayer/Zeneca	6vs12M	?	3 (3)	—	—	—	—
FDA	6vs12M	?	2 (2)	—	—	—	—
additional							
JPMA	3vs12M	22 [#]	0	18		4	—
additional							

* : Survey of reports published in Japanese Toxicology Journals in 1985-1992 by a subcommittee of JPMA in 1992.

[#] : Survey of reports published in Japanese Toxicology Journals in 1992-1995 by a subcommittee of JPMA in 1996.

() Eighteen cases ⁴⁾ pointed out by the FDA as evidence of necessity for 9M study.

Table 2. Results of Questionnaire against Toxicologists in the Pharmaceutical Industry.**JPMA Survey (88 companies) in 1987**

Toxicological Findings	Observed in 12-Month Dog Studies
within 6 months	51 studies (94%)
after 6 months	2 studies (4%)
at 12 months	1 studies (2%)

CMR Survey (32 Companies) in 1993**New Information Produced by 12-Month Studies in the Dog**

No experience	43 toxicologists
A few experience	2 toxicologists

JPMA Survey (85 Companies) in 1995**Adoption of 9-Month Dog Study**

Agree	20 Companies (24%)
Disagree	65 Companies (76%)

study against the leading pharmaceutical companies in the world. The JPMA argued that no drugs induced new and toxicologically significant findings in dogs after 3 or 6 months of dosing based on results of additional survey (22 drugs) of recent 3/12-month toxicology studies in 7 Japanese Journals (Table 4). At this meeting, measures for regulatory parties (FDA, MHW and EC) were the predominant items for discussion. Further analysis of detailed data for 18 drugs put forward by the FDA as evidence for the necessity of a 9-month period and their thorough evaluation were decided as an immediate object of attention. For this purpose, there will be a meeting in Copenhagen in September of this year.

It is considered that the 9-month duration has not always been evaluated and proposed from the scientific viewpoint. There are not a few concerns that 9-month studies are performed because of no or little experience. Many toxicologists are troubled about what duration of short-term toxicity studies should be combined with 9-month studies. Furthermore, the apparent benefits of a 9-month study as compared with a 12-month study are not clear. In addition, the FDA representative in the ICH EWG of Topic M3, the timing of non-clinical safety studies for

Table 3. Eighteen cases (Drugs and Toxicological Findings) Pointed out by the FDA as Evidence of Necessity for a 9-Month Study.

Database	Drugs (Findings)
JPMA 5 compounds	Benzodiazepine derivative (Hypertrophy & vacuolation in adrenal glomerular zone, Coma), Dihydropyridine Ca-antagonist (Gingival hypertrophy), Recombinant erythropoietin (Polycythaemia), Low molecular heparin (Cloudy foci in lens), Bone calcium regulator (Abnormal ossification)
CMR 3 compounds	Antihypertensive (Hypertrophy & vacuolation in adrenal glomerular zone, Hypertrophy & vacuolation in renal tubules), Endocrine (Cataract), NSAID (Interstitial nephritis)
FDA 7 compounds	Alzheimer's (Colon nodules), Antidepressant (Deaths due to cardiac arrhythmia), Anti-psychotic (Arteritis), NSAID (Interstitial nephritis), Antihypertensive (Hepatitis), Non-steroidal antiandrogen (Hepatotoxicity), Anticholinesterase (Tardive dyskinesia)
Bayer 2 compounds	Benzodiazepine derivative (Convulsions), Ca-antagonist (Gingival hyperplasia)
Zeneca 1 compound	β -Blocker (Hypertrophy in adrenal glomerular zone, Renal toxicity)

Table 4. Additional JPMA Database

Therapeutic class	No. of compounds surveyed
Diuretic	1
Antihypertensive	
Calcium antagonist	4
ACE-inhibitor	1
Potassium channel opener	1
Antihyperlipemia	1
Hormone (including antihormone)	4
Antiallergic	3
Antiemetic	1
Antiulcer	1
Antipsychotic	
MAO-inhibitor	1
Miscellaneous	4
Total	22

A subcommittee of JPMA (19 toxicologists) surveyed reports published in 7 Japanese toxicology journals in 1992-1995

the conduct of human clinical trials, has requested 12-months as the longest duration for non-rodent repeated-dose studies.

We suspect that new complications may arise if a 9-month period is adopted. We should pay attention to results of re-analyses of 18 drugs data by regulatory parties, and to its contribution to adoption or rejection of a 9-month.

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- 8) “Guidelines for Toxicity Studies of Drugs”, Notification No. 88 of the New Drugs Division of Pharmaceutical Affairs Bureau in MHW, August 10, 1993.
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