The Continuing History of the Safety of Medicines

Alasdair Breckenridge
Medicines & Healthcare products Regulatory Agency

APEC Japan 2006

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UK - Arsenic Act of 1851 and Pharmacy Act of 1868

US - Food, Drug and Cosmetic Act of 1938 followed the sulphanilamide – ethylene glycol scandal of 1937

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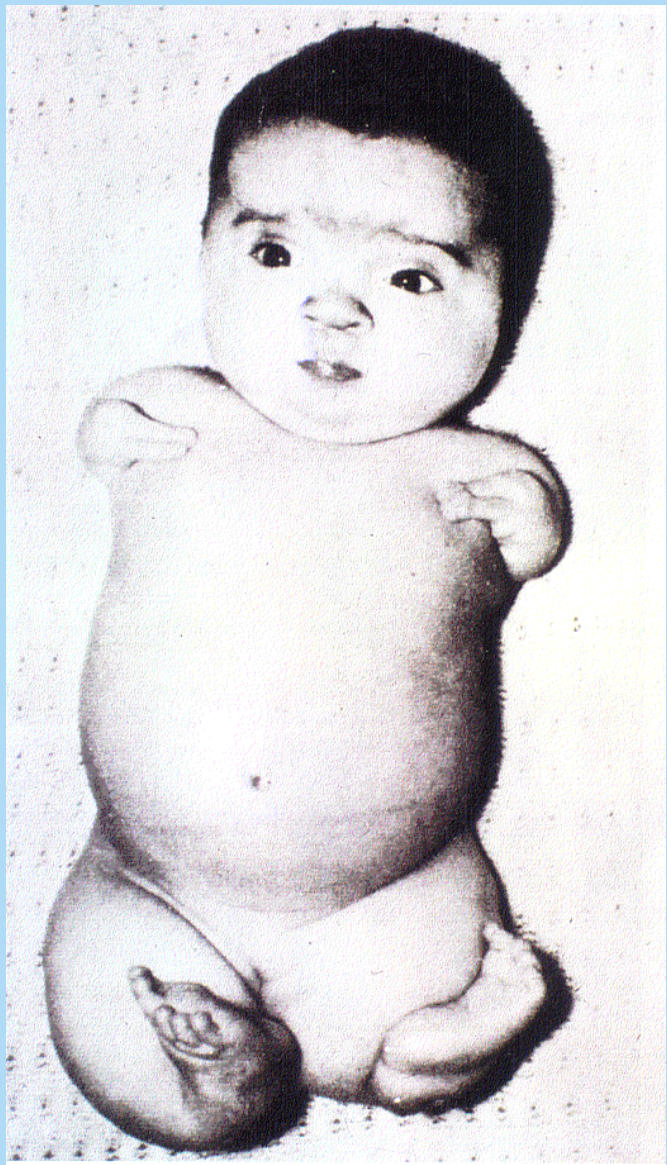

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Post marketing studies in UK

115 Studies requested from 1986 – 2005

- 1/3 completed
- 1/3 ongoing
- 1/3 not started

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MERCK

News Release

Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept. 30, 2004 – Merck &. Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.

"We are taking this action because we believe it best serves the interests of patients," said Raymond V. Gilmartin, chairman, president and chief executive officer of Merck. "Although we believe it would have been possible to continue to market VIOXX with labeling that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take."

APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (three years) of treatment with VIOXX on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenoma. The trial enrolled 2,600 patients and compared VIOXX 25 mg to placebo. The trial began enrollment in 2000.

- more -

VIOXX® (rofecoxib) is a registered trademark of Merck & Co., Inc.

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Early information

- Phase 1 placebo controlled trial of a monoclonal antibody
- Trial approved by both UK and German medicines regulatory authorities
- 8 Healthy volunteers, 6 of whom were given active drug

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Clinical events (1)

2 hours

- All 6 subjects acutely unwell
- Headache, diarrhoea and vomiting, diffuse muscle pains
- swelling of face and limbs
- disturbance of consciousness, hypotension

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Clinical events (2)

16 hours

- all critically ill, in intensive care
- pulmonary infiltrates and lung injury
- renal failure
- disseminated intravascular coagulation
- severe lymphocyte depletion

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Possible causes

- contamination of test material
- wrong dose
- other error in protocol
- ill understood pharmacology

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Treatment

- cardiopulmonary support
- renal dialysis
- prednisolone
- anti interleukin 2 receptor antagonist antibody

Course of illness

- all six survived, one developed gangrene of extremities

Diagnosis

- multiple cytokine release syndrome

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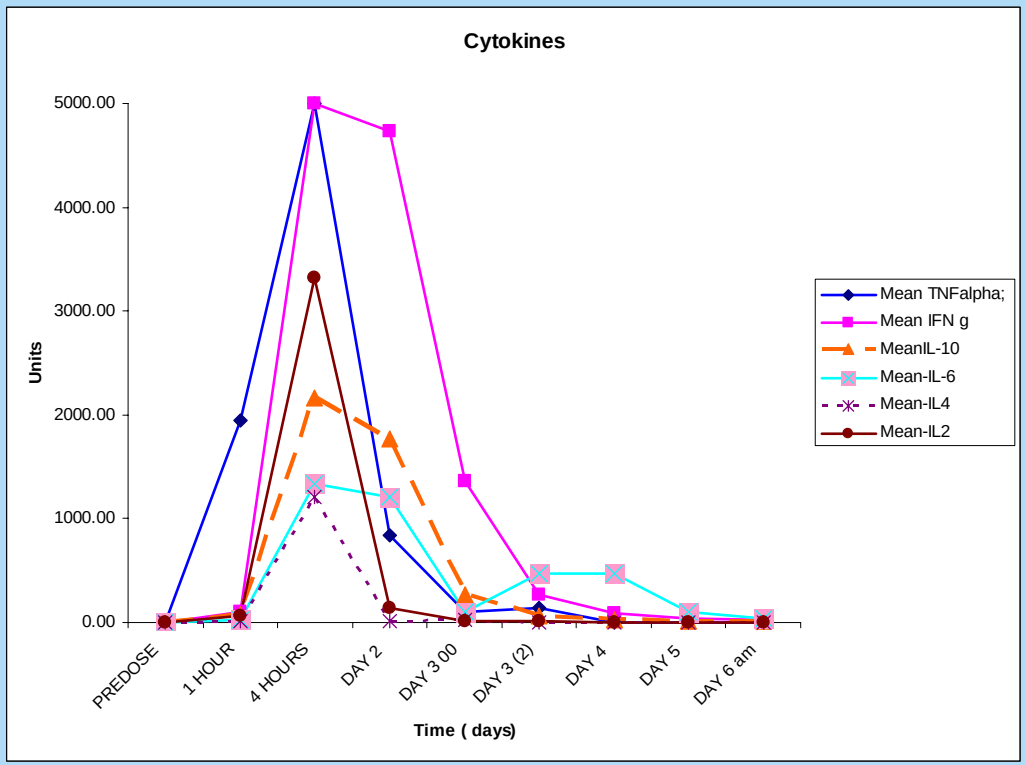

Summary of Cytokines values from an Independent lab:

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TGN 1412

- Humanised mAb specific for CD 28 receptors on T cells
- agonist at CD 28 receptors
- identical binding characteristics in man and cynomolgus monkey
- initial dose in man 500 fold less that NOAEL in monkey

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Remit of Expert Scientific Group (ESG)

To consider what may be necessary in the transition from preclinical to first in man phase 1 studies, and in the design of these trials with specific reference to:

- biological molecules with novel mechanisms of action
- new agents with highly species specific actions
- new drugs directed towards immune system targets

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Interim report of Expert Scientific Group

www.dh.gov.uk/consultations

Clinical details

Suntharalingam G et al .

NEJM. 355, 1018-1028 (Sept 7, 2006)

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How should the initial dose be calculated?

How should the first subjects be selected?

How should the trial be conducted?

How should previous relevant information be accessed?

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Dose (1)

NOEL – No Effect level

NOAEL – No Adverse Effect Level

Correction factors

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Dose (2)

TGN 1412

NOEL – 0.3 mg kg -1

NOAEL – 50 mg kg -1

Correction factors
Initial dose in man – 0.1 mg kg -1

(500 fold less than NOAEL)

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Dose (3)

Factors to be taken into account

- Novelty of agent
- Mechanism of action
- Species specificity
- Dose response in human and animal cells
- in vivo animal models
- Receptor occupancy in relation to concentration
- Calculated exposure of target cells in humans in vivo

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Dose (4)

Minimum Anticipated Biological Effect Level (MABEL)

- Initial dose is that required to reach lowest point on dose response curve in man
- Calculated from information on:
  - human receptor occupancy
  - cellular dose response studies
  - studies in animal models with similar agents

TGN 1412
MABEL-0.005mg.kg-1
(20 fold decrease)

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Selection of subjects (1)

- Inherent risk of agent
- Presence of target in healthy subjects
- Value of information in HV or patients

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Selection of subjects (2)

Healthy volunteers

- PK and PD results more reproducible
- immune system less vulnerable to interference
- non-cytotoxic mAb

Patients

- PK influenced by IgE levels
- cytotoxic mAb

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Conduct of study

- Preclinical information
- Cohort or sequential dosing

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Preclinical information

Chemical based drug

- Repeat dose toxicity in 2 species (one non rodent) for two weeks

Biological

- Animal model critical; must demonstrate pharmacodynamic effect
- mAb-homologous target should be expressed
  - if no model, human cells or transgenic animal model

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Cohort or sequential dosing

Sequential if:

- mAb has novel mechanism of action
  - agonists of immune system
  - modulators of cytokines
- mAb addresses target with no animal model
- mAb has novel structure
  - engineered Fc parts
  - divalent

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Access to previous information

- EU Clinical Trials Directive
- Company data
- Unpublished

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Conclusions

- Regulatory implications of TGN 1412
- Good track record of safe conduct of phase 1 clinical trials
- Importance of discovery and investigation of new biological medicines

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