



# Pharmacovigilance needs and opportunities for ENCePP

Hubert G. Leufkens

# Declaration of interests

- Chairman of the Dutch Medicines Evaluation Board (MEB), since mid 2007.
- Co-opted member of CHMP PhVWP, since 2006.
- Member of ENCIAG on behalf of PhVWP
- Professor of Pharmacoepidemiology, Utrecht Institute of Pharmaceutical Sciences, 0.4 FTE.
- This talk reflects my personal views; I am being inspired and challenged on a daily basis by many colleagues from these 'environments'.

# Principles-based versus rule-based regulation



Pogatetz is booked after a furious rant at referee Vink who awards Croatia a penalty in the 4 minute.

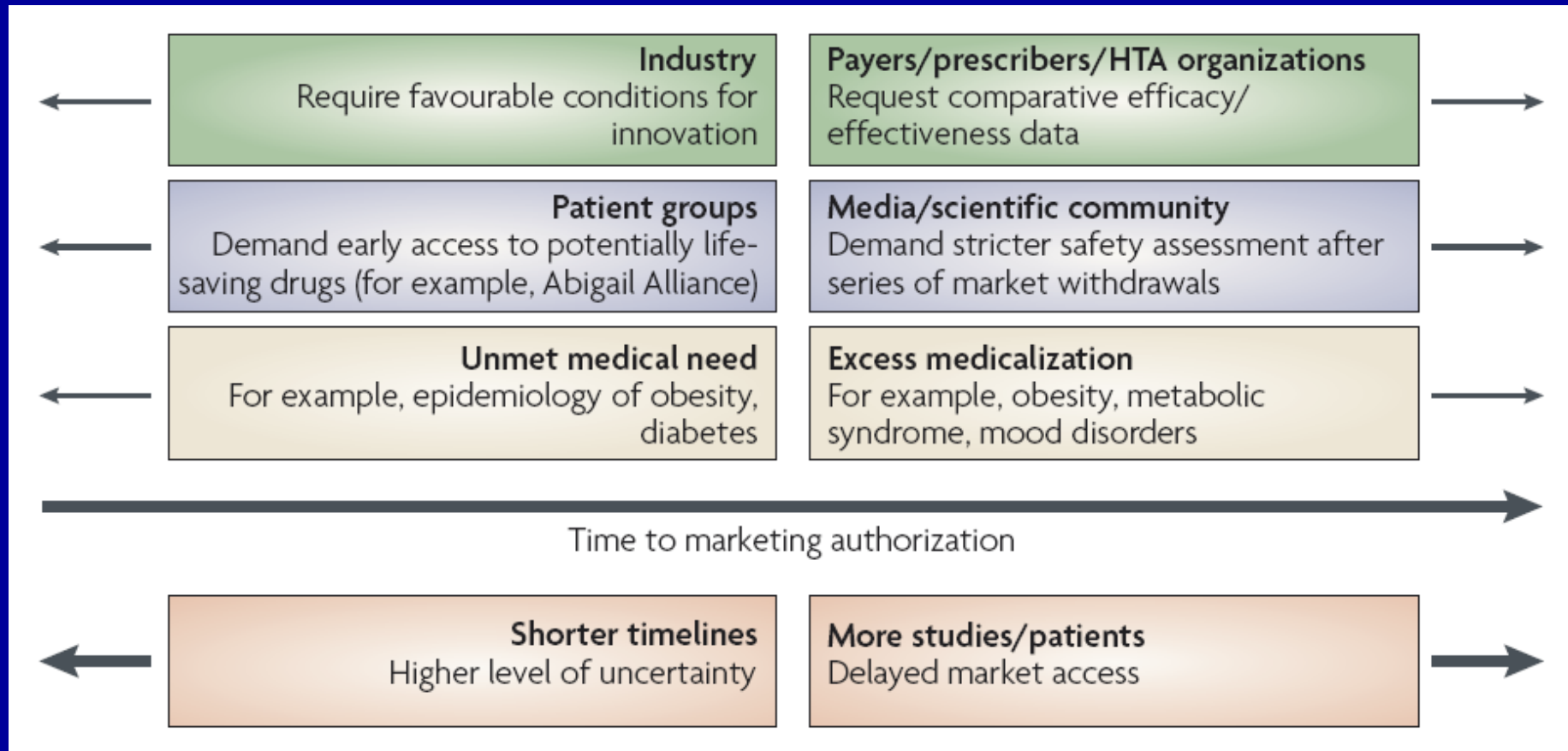
... Football, like most American sports, is heavily rule-bound.

... Soccer is a more principles-based game. There are fewer rules, and the referee is given far more authority than officials in most American sports to interpret them and to shape game play and outcomes...

A bad or biased ref can ruin a soccer match in the way that no bad ref can ruin a football match, the lesson being that regulator independence is key in a principles system...

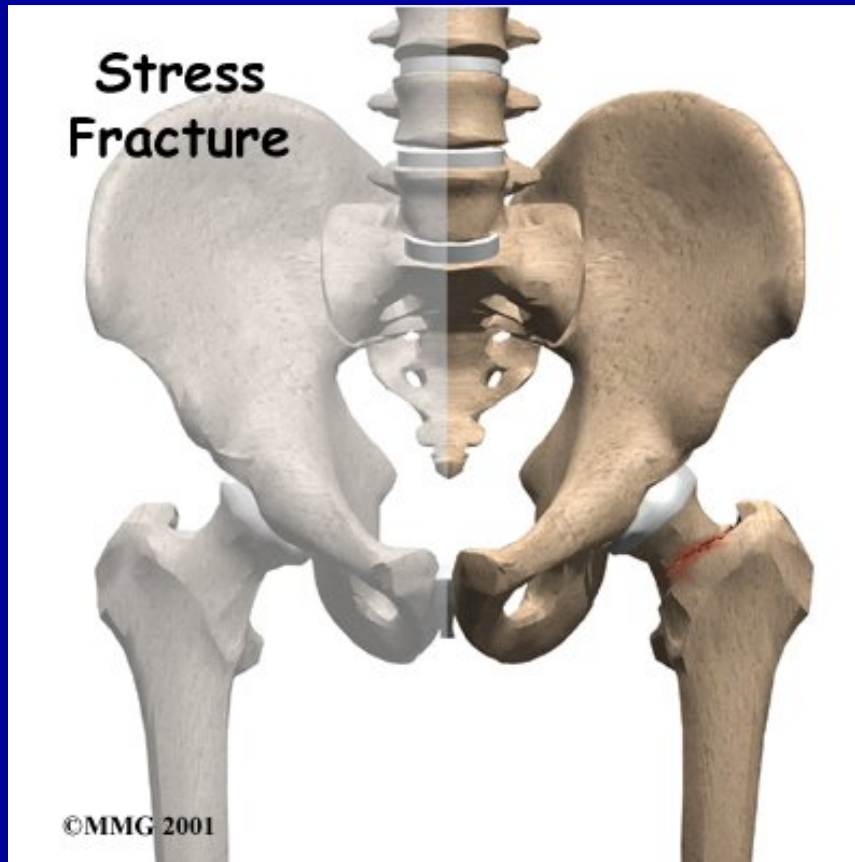
*Economist. Metaphor of the day, April 21, 2008*

# Regulatory science agenda

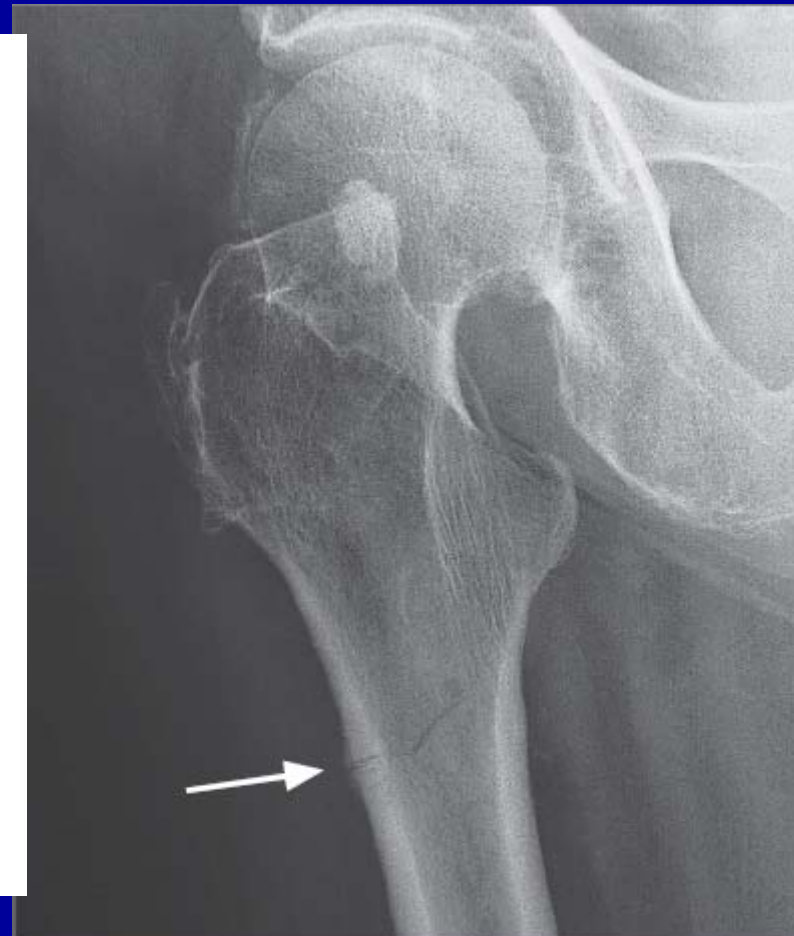


Eichler H-G, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data: a mounting dilemma. *Nature Drug Disc* 2008; 7(10): 818-26.

# Biphosphonates and risk of stress fractures



Kwek E.B.K et al. More on atypical fractures of the femoral diaphysis. N Engl J Med 2008; 359: 316-318.



**Figure 1.** Radiograph Showing a Subtrochanteric Stress Fracture Associated with a Typical Cortical Stress Reaction.

# MABs and risk of multifocal leukoencephalopathy (PML)

## Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union

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Thijs J. Giezen, PharmD

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Aukje K. Mantel-Teeuwisse, PhD

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Sabine M. J. M. Straus, MD, PhD

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Huub Schellekens, PhD

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Hubert G. M. Leufkens, PhD

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Antoine C. G. Egberts, PhD

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**B**IOLOGICALS, DEFINED AS PRODUCTS of which the active substance is produced by or extracted from a biological source, represent an important and growing part of the therapeutic arsenal.<sup>1</sup> In the United States, the first bio-

**Context** Biologicals are a relatively new class of medicines that carry specific risks (eg, immunogenicity). However, limited information is available on the nature and timing of safety problems with their use that were identified after approval.

**Objective** To determine the nature, frequency, and timing of safety-related regulatory actions for biologicals following approval in the United States and/or the European Union.

**Design and Setting** Follow-up of a group of biologicals approved in the United States and/or European Union between January 1995 and June 2007. Vaccines, allergenic products, and products for further manufacture and transfusion purposes were excluded.

**Main Outcome Measures** Nature, frequency, and timing of safety-related regulatory actions defined as (1) dear healthcare professional letters (United States) and direct healthcare professional communications (European Union), (2) black box warnings (United States), and (3) safety-related marketing withdrawals (United States and European Union) issued between January 1995 and June 2008.

JAMA 2008; 300: 1887-1896.

# Antipsychotics in the elderly and increased mortality

## Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D., Michael A. Fischer, M.D., Helen Mogun, M.S., Daniel H. Solomon, M.D., M.P.H., and M. Alan Brookhart, Ph.D.

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### ABSTRACT

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#### **BACKGROUND**

Recently, the Food and Drug Administration (FDA) issued an advisory stating that atypical antipsychotic medications increase mortality among elderly patients. However, the advisory did not apply to conventional antipsychotic medications; the risk of death with these older agents is not known.

#### **METHODS**

We conducted a retrospective cohort study involving 22,890 patients 65 years of age or older who had drug insurance benefits in Pennsylvania and who began receiving a conventional or atypical antipsychotic medication between 1994 and 2003. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation

From the Department of Psychiatry (P.S.W.) and the Division of Pharmacoepidemiology and Pharmacoeconomics (P.S.W., S.S., J.A., M.A.F., H.M., D.H.S., M.A.B.), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston. Address reprint requests to Dr. Wang at the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont St., Suite 3030, Boston, MA 02120, or at [pwang@rics.bwh.harvard.edu](mailto:pwang@rics.bwh.harvard.edu).

N Engl J Med 2005;353:2335-41.

# Anchors for needs and opportunities for ENCePP collaboration I

<b>Biphosphonates &amp; stress fractures</b>	<b>MABs and risk of PML</b>	<b>Antipsychotics and mortality</b>
Misclassification of diagnosis	Rare, difficult to see, but very severe	Different pathways to outcome
Duration of use, patterns of use	Outcome masked by indication	Patterns of use, off-label prescribing
Need for bone quality data, biomarkers	Ascertainment and traceability exposure	Class effect, differential risk
Confounding by indication	Differential weighing of B/R per indication	Confounding by underlying disease
Etc.	Etc.	Etc.



# **Anchors for needs and opportunities for ENCePP collaboration II**

- Regulators are in need of the strongest evidence available for B/R assessment.
- The three cases discussed are 'real' and represent a window of opportunities for Pan-EU research
- There is no single approach, centre or database that can solve all the issues.
- The concept of ENCePP deserves full commitment and the willingness to learn and share.