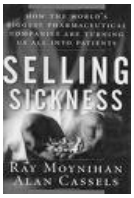
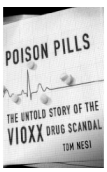
Promoting The Integrity of Pharmaceutical Research: What Role for Academia?

Trudo Lemmens
Faculties of Law and Medicine
Joint Centre for Bioethics
University of Toronto
Trudo.lemmens@utoronto.ca

Dominant Discourse Academia-Industry Partnerships

- Partnerships are motor for new health product (& economic) development
  - Align agendas of industry—funding agencies-academia
  - Promote collaborative research & health product development
- Changing Nature Academic Institutions
  - Co-funding arrangements
  - Commercialization Hubs (e.g. MaRs)
  - Industry-funded Research & Education, industry-funded Chairs





Drug Regulatory Context

- Focus on Initial Drug Review and Approval: based on limited data of safety and effectiveness; creates public expectation that pharmaceuticals on market are safe and effective
- Information on post-marketing drug safety & effectiveness: largely provided by industry
- Clinical practice (including **Off-Label Prescription**) largely informed by medical literature and CPGs, with significant role of academic research community

"Problems Current System"

Ferberg et al. An.Intern.Med. 2006

1. Initial Review: too limited
2. PMS: out of FDA's control; lack of authority to enforce PMS by companies
3. Lack of accountability for suppression or delaying unfavourable trail information
4. Structure of FDA: Potential Conflict may prevent action post marketing
5. Lack of expertise FDA drug safety panels

6-10 independence; underreporting adverse drug reactions; slow withdrawals

How Reliable is Publicly Available Information on Drug Safety and Effectiveness?

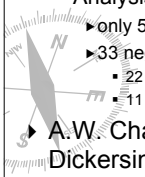
- Subtle impact of source of funding clinical trials
- Troublesome Publication Practices Involving Academic Researchers

Subtle Impact of Interactions with Industry: Bias

- Source of Funding Impacts on Outcome of Research: industry funded research more likely to be favourable to products of industry sponsors
- Meta-analyses by
  - **Bekelman** *et al.* (JAMA 2003)
  - **Lexchin** *et al.* (BMJ 2003)
  - **Schott** *et al*. (Dtsch Arztebl Int 2010):

Publication Bias

- E.H. Turner et al., "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy" 2008 *NEJM* 358: 252-60.
  - Published literature: 94% studies positive
  - Analysis 74 FDA registered studies:
    - only 51% positive
    - 33 negative studies:
      - 22 not published
      - 11 ***published conveying a positive outcome***
- A.W. Chan *et al* (JAMA 2004; *CMAJ* 2004); Dickersin (*Contr. Clin. Trials*); Lee (PLoS)

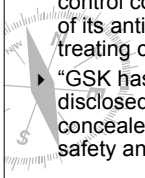


Scientific Publications Strategy: Managing Reputation, Clinical Trial Results and Commercial Relevance, Best Practices LLP ($3,695)

"While picking and choosing favorable findings may have been acceptable a decade ago it is now considered unethical and potentially illegal."

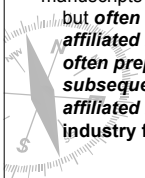
A.G. New York v. GlaxoSmithkline: June 2004

- Elliott Spitzer (AG): "GSK has engaged in repeated and persistent fraud by misrepresentation, concealing and otherwise failing to disclose to physicians information in its control concerning the safety and effectiveness of its antidepressant medication paroxetine in treating children and adolescents."
- "GSK has allowed positive information …to be disclosed publicly, but has withheld and concealed negative information concerning the safety and effectiveness"



[redacted]

manuscripts … were ***authored by sponsor employees*** but ***often attributed first authorship to academically affiliated investigators…*** . ***Review manuscripts were often prepared by unacknowledged authors and subsequently attributed authorship to academically affiliated investigators*** who often **did not disclose industry financial support** (*JAMA* 2008: Vol.299)



Draft Version and Final Version of Article Describing the Results of Protocol 078

Rofecoxib does not delay the onset of Alzheimer's disease: results from a randomized, double-blind, placebo-controlled study

External author?, W.H. Visser[1], E. Yuen[1], C. Assaid[1], M.L. Nessly[1], B.A. Norman[1], C.C. Baranak[1], C.R. Lines[1], S.A. Reines[1], G.A. Block[1] on behalf of the Rofecoxib Protocol 078 study group

A Randomized, Double-Blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment

Leon J Thal[1], Steven H Ferris[2], Louis Kirby[3], Gilbert A Block[4], Christopher R Lines*[,4], Eric Yuen[4], Christopher Assaid[4], Michael L Nessly[4], Barbara A Norman[4], Christine C Baranak[4] and Scott A Reines[4], on behalf of the Rofecoxib Protocol 078 study group[5]

[1]University of California, San Diego, CA, USA; [2]New York University School of Medicine, New York, NY, USA; [3]Pivotal Research Centers, Peoria, AZ, USA; [4]Merck Research Laboratories, West Point, PA, USA

Ross, J. S. et al. JAMA 2008;299:1800-1812.

October 1999 E-mail Between Representatives of Scientific Therapeutics Information Inc and Merck Co Inc Discussing Contracted Publications Related to Rofecoxib

Dear Susan,

At the request of John Romankiewicz, I am providing you with an update on development and estimated delivery dates for various publications related to VIOXX that STI is working on.

1) Rofecoxib for the Treatment of Pain: Role of COX-2 Inhibitors for the Treatment of Nonmalignant Pain
- intended author: [redacted]
- intended journal: Analgesia
- estimated delivery of Draft 2 to Merck: 10/22

2) Clinical Implications of Drug Interactions with COX-2 Inhibitors
- intended author: [redacted]
- intended journal: Pharmacotherapy
- estimated delivery of Draft 2 to Merck: 10/22 (John Romankiewicz recently e-mailed you Draft 1 of this manuscript)

3) Overview of Clinical Pharmacology and Clinical Experience with Rofecoxib
- intended author: [redacted]
- intended journal: American Journal of Medicine or Archives of Internal Medicine
- estimated delivery of Draft 1 to Merck: 11/5

4) Review of Pharmacology and Clinical Experience with Rofecoxib for Osteoarthritis
- intended author: [redacted]
- intended journal: Journal of Rheumatology
- estimated delivery of Draft 1 to Merck: 10/29

5) Osteoarthritis in the Elderly: The Role of COX-2-Specific Inhibitors
- intended author: [redacted]
- intended journal: Geriatrics
- Draft 1 provided to Merck (C. Yarbrough) 9/27 - await comments; this manuscript cannot be sent via E-mail at this time as it is being actively edited based on additional internal comments; please call if you would like a copy FAXed to you

6) Changing Paradigm for Management of Osteoarthritis
- intended author: [redacted]
- intended journal: Journal of Osteopathic Medicine or Journal of Family Practice
- estimated delivery of Draft 1 to Merck: 11/12

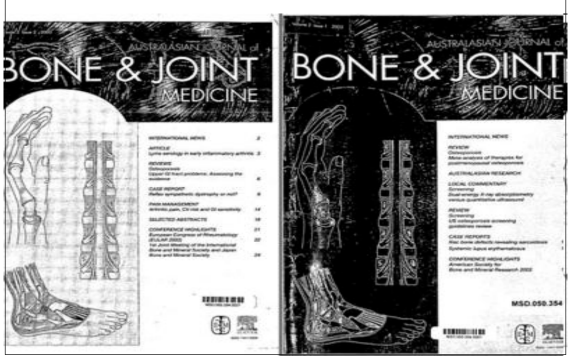
7) Pharmacoeconomic Considerations in Treating Osteoarthritis: COX-2-Specific Inhibitors Versus NSAIDs
- author (confirmed): [redacted]
- intended journal: Journal of Managed Care
- extended outline provided to Merck (C. Yarbrough) and author 9/27 - copy attached for your reference. Outline approved by author; no comments received from Merck to date
- estimated delivery of Draft 1 of manuscript to Merck: 11/5

8) Managed Care Perspective on the COX-2 Inhibitors
- intended author: [redacted]
- intended journal: Managed Care
- estimated delivery of Draft 1 to Merck: 11/19

If you have any questions or require additional information at this time, please do not hesitate to contact me.

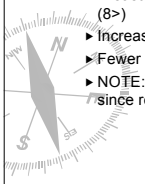
Ross, J. S. et al. JAMA 2008;299:1800-1812.

The Australasian Journal of Bone and Joint Medicine



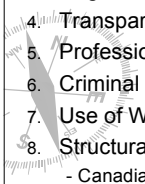
Consequences are serious

- D. Graham : 'VIOXX may have caused 140,000 serious injuries or deaths between 1999-2004'
- Hormone Replacement Therapy: NIH study 2002
  - 2 most common HRT: 62 million prescriptions 2000
  - Breast cancer, ovarian cancer, stroke, pulmonary embolism (8>)
  - Increased risk of heart disease (7> per 10,000)
  - Fewer hip factures (5<) and colon cancer (6<)
  - NOTE: statistics US confirm drop of 8,6% in breast cancer rates since reduction hormone replacement prescription



Remedy: Comprehensive and Integrated Approach

1. Conflict of Interest Rules
2. Clinical Trial Registration and Results Reporting
3. Strengthen Power & Independence Drug Regulator
4. Transparency Financial Relations: Sunshine Acts
5. Professional & Academic Sanctions
6. Criminal Law
7. Use of Whistle-blowers: US Qui Tam procedures
8. Structural Reform: PMS system
   - Canadian Drug Safety and Effectiveness Network



2. Trial Registration & Results Disclosure

(Krleza-Jeric K, Lemmens T *et al*, PAHO J. Pubic Health)

US FDA Amendment Act 2007

- Expands ClinicalTrials.gov Registry: obligation to register clinical trials (exc. Phase I)
- Obligatory results reporting of clinical trials of approved drugs and devices (basic results)
  - "Basic" Results: Baseline Characteristics, Key Outcomes, Statistical Analyses (and Adverse Events)
- Serious Penalties for non-compliance
  - Withdrawal of funding
  - Penalty of 10,000 per violation/per day

Limits of Registration

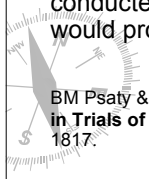
- Enforceability registration requirement?
  - ICMJE: enforcement related to publication
  - WHO: no enforcement other than 'moral authority'
- Penalties Necessary: Register Trials for Serious & Life-Threatening Diseases US: significant non-compliance (prior to FDA Amendment Act!): Only 48% of 127 cancer trial protocols sponsored by pharmaceutical companies were submitted to the registry (Derbis J, et al (2003): reported by Turner PloSMedicine 2004.

Limits of Current Registration

- **Access to protocol and full data?**
  - S. Vedula, L. Bero et al. (2009 NEJM 361): comparison internal research reports – published reports Neurontin
    - Several reports not published
    - 6/20 identified primary outcomes not in published report; 4/20 reported as secondary outcomes; new primary outcomes; underreporting of negative outcomes
  - " [these] reporting biases increase the likelihood that interventions will appear to be effective when they are not" … "registration should include registration of the full study protocol and amendments"
- **Sponsor still controls clinical trials**

New Approaches Necessary

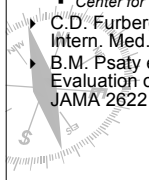
« New approaches for the conduct, oversight, and reporting of industry-sponsored trials, are necessary. A clinical trials system in which sponsors fund the trials that are conducted by independent investigators would provide additional protections."



BM Psaty & KR Kronmal, "**Reporting Mortality Findings in Trials of Rofecoxib... »** *JAMA.* 2008;299(15):1813-1817.

7. Independent Drug Safety Agency

- W. Ray & M. Stein, "Reform of Drug Regulation—Beyond an Independent Drug-Safety Board" 2006 *NEJM* 354: 194-201: New Independent Drug Agency, funded by tax on pharmaceuticals:
  - *Center for Drug Approval*
  - *Center for Post-Marketing Studies*
  - *Center for Drug Information*
- C.D. Furberg et al. "The FDA and Drug Safety" 2006 Arch. Intern. Med. 166: 1938-42.
- B.M. Psaty et al. "Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions" 2004 JAMA 2622



Canada's Drug Safety and Effectiveness Network (DSEN)

- Network of centres for PM pharmaceutical research
- Mandate:
  - provide strategic direction and common research agenda, in collaboration with national partners
  - organize funding
  - govern independent PM research of centres
- Funding federal government: 35 million per 5 years

Good Governance Framework

(Ferris & Lemmens, *Open Med*. Forthcoming)

Key Principles DSEN and Participating Research Centres

- Transparency and Openness
- Accountability
- Independence
- Commitment to Scientific Integrity
- Freedom of Action

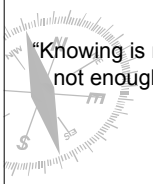
Challenges DSEN

- Funding: limited when compared with industry
- Stability of Funding?
- Governance and Independence from Industry-Funding Agency Connections
- How Stringent Can COI Rules Be?

Conclusion

- Strengthen Regulatory Tools
- Promote Transparency
  - Financial Relations
  - Research Results
- Use of Existing Legal Tools
  - Separation of academic & regulatory interests AND RESEARCH CONDUCT from industry interests
  - Enhance public interest research by reinvigorating partnership public interest science and academic sector

"The piecemeal organizational modifications and short-lived programmatic initiatives of the past and the current, seemingly fragmented and reactive initiatives . . . are not sufficient to meet the need to improve postmarket drug safety activities and protect the public health better." **Institute of Medicine *The Future of Drug Safety* 2007**



"Knowing is not enough; we must apply. Willing is not enough; we must do." Goethe