Promoting Pharmaceutical Treatment in a Context of Knowledge Deficit: the case of the CINP's Task Force on Depression

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Task Force Collegium Internationale Neuro-Psychopharmacologicum

- CINP
  - Devoted to Promotion of Research, Education & applications of Neuropsychopharmacology to the clinic
  - Main Task: extend knowledge of drugs to improve management of mental disorders
- Task Force on Antidepressant Medication: 2004-06
  - 15 experts in psychiatry, psychopharmacology, public health, economics, family care; + Advisors in various countries
  - Approved report published in International Journal of Neuropsychopharmacology 2007; translated in Chinese, French, Russian & Spanish;
  - Report presented at meetings in Caracas, Munich, Paris, Shanghai & St. Petersburg + national meetings subsequently 2007-2008

Methodology

- Review of the Published Literature on anti-depressants
- Review of cost-effectiveness (economic analysis)
- Submission of the Draft Review to experts for comments (translated and discussed at meetings)
- Additional chapter on diagnosis of depression, epidemiology, . . . and on other treatments
- FOCUS: Review of the 'Evidence", with "particular attention to results obtained in randomized control trials"

Acknowledgment of Limitations

"A statistically significant difference, however, is not always equal to clinical meaningful difference; nor is the evidence obtained in research the only evidence to consider in treatment decisions. For that reason, this review was developed in consultation with leading mental health experts, representatives of family organizations and specialists in other medical disciplines other than psychiatry"

Acknowledgment of Limitations

- "Some but not all analyses suggest that SSRI treatment is more cost-effective than treatment with TCAs"
- "Most studies are based in developed countries, and given the fundamental differences in health systems across the world, it is difficult to know whether their findings can be generalized to other countries."

Acknowledgment of Limitations

- Published literature & bias
- "Efficacy Gap": between outcome of trials & outcome in primary care
- Problems with diagnostic criteria and broad categorization of mental illness
- Lack of publication of failed trials
- Most trials: Europe & N.America
- Most trials focus on major depression

Yet: Overall Recommendations

- Emphasis on depression as a significant and under-diagnosed public health threat
- Emphasis on efficacy of new anti-depressants and their relative safety
- Emphasis on cost-effectiveness of prescribing SSRIs over other forms of depression treatment
- Emphasis on need of education and awareness

Specific Recommendations

1. To employ the report as a platform for the development of training programs and guidelines concerning the recognition and treatment of depressive disorders

2. To develop specific guidelines concerning the use of antidepressant medication & to bring them to attention of practitioners worldwide (help of WHO)

3. To develop materials that will be suitable for the correct information of the general public about depressive disorders and their treatment

‘Integration’ of critical voices

“Because other difficult issues *such as the existing problem of misconduct in clinical research cannot be resolved completely*, the CINP task force decided to report David Healy's view in full to empower readers to draw their own conclusions about these issues.”

Justification for focus on 'Published Literature"

"Some, but not all companies have now committed themselves to an open database policy of supplying information regarding all controlled, company-sponsored trials… However, using this information from some companies but not from others would also *unfairly* bias the results and views expressed here." (p. S 13)

Critics

- David Healy: ‘dissenting opinion’ integrated in full in appendix: Critique of ‘epidemiological’ approach to anti-depressant prescription
  - Large placebo effect & limited treatment effect
  - Unclear who benefits from SSRI treatment
  - Exposure of large group of patients to potential harm for benefit of few
- R.A. Belmaker (president elect CINP):
  - Treatment effect; lack of knowledge international context
  - Conflict of Interest Issues & problematic reliance on Published Literature

COI Statement CINP Task Force

- Unrestricted Grants from Bristol-Meyer Squibb, Eli Lilly, Fornest Labs, GSK, Lundbeck, Servier, Wyeth
  - Cost of travel, meetings, administrative support
- Members: 20 relations with industry (speaker fees; consultancy, contracts, grants, stock, patent); 4 members declare no conflicts

Critique Thomas Ban

- Only based on published evidence
- Of 1,600 references: only 5% published prior to 1990s
- Discriminate treatment of tricyclic antidepressants (TCAs; older standard medication)
- Treatment of TACs as homogeneous group; yet:
  - Reboxetine pharmacologically homologous with desipramine (one of first TCAs)
  - Other SSRIs homologous with three older TCAs
- SSRIs not indicated for treatment of severe depression
- Underplaying of risk of suicide with SSRIs & suggestion that warning about suicidality interferes with diagnosis & treatment

Critique Ban

"By reinforcing the notion that depression-induced disability could be curbed by hunting down and treating all depressed patients with anti-depressants, the task force distracts attention from the need of the field to develop a methodology for the identification of the treatment-responsive subpopulations to each drug in the broad diagnostic categories of major depressive disorder and depressive episode"

Critique Ban

"By summarizing studies that were conducted to create a place in the market for each newly introduced antidepressant the task force has posted all the recommendations industrial marketing would have liked to post but was not allowed to do, and provided a guide for physicians to use and regulators to accept the newest and most expensive drugs"

Comment on Task Force Report, Int'l. J. Neuropsychoph. 2008; 11, 583-585.

The Problem of Hidden Data

Pharmaceutical Clinical Trials Data

- Historical Context: data required since 1950/60s for market approval of products
- NOT essential component of drug development
- NOT the only form of evidence of safety and efficacy!
- Increasingly produced by specialized Clinical Trials Industry: service-provider to Pharma

Interesting example of how REGULATORY REQUIREMENTS HAVE

- SHAPED HOW WE THINK ABOUT DRUG SAFETY AND EFFICACY
- Contributed to MARKET CONTROL OVER KNOWLEDGE

Key Aspect of the Problem

- ***Control of Industry over Production and Distribution of Knowledge:*** Design, Conduct, Analysis, Publication, and Distribution of Clinical Trials Reports
  - Skewed clinical trial design
  - Hiding & misrepresentation of clinical trials data
  - Manipulation of scientific literature
  - Aggressive promotion of unsafe (off-label) prescription
- Limited control regulatory agencies:
  - limited evidence required for approval of pharma products
  - little control on public presentation data
  - **Over-emphasis & Reliance on Market-Entry CT data**

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."
- "Scientific publications are an essential tool for both clinical and commercial purposes, as they are intended to influence the target audience…"

Reviews and Overviews

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

30 Reports of comparative efficacy clinical trials funded by industry

- 90% overall outcome favourable to drug sponsor
- Sources of bias:
  - Dose ranges & escalation schedules: stepwise or faster (efficacy & side-effects)
  - Vagueness of entry criteria and study population
  - Statistics and Methods
  - Reporting and wording of results
  - Multiple Publishing (salami-slice publications)

Am. J. Psych. 2006: 163(2): 185-194

Ioannidis: "Clinical Trials: What a waste?" BMJ 2014

- Published trials problems:
  - Original outcomes often unreported
  - Manipulation analysis & reporting
  - Results inflated & spin towards favourable conclusions
  - Harms underplayed
- For many trials: questions asked, comparisons and outcomes clinically irrelevant

Are Your Medications Safe?

The FDA buries evidence of fraud in medical trials. My students and I dug it up.

By Charles Seife

Regulatory findings of Fraud not acted upon & not shared

- 600 clinical trials with failed FDA inspection: only 100 traceable to identifiable study
- 78 Scientific publications based on studies with significant FDA identified problems, including fraud
  - Only 3 papers refer to problems
- Even FDA advisory committee members not informed

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

74 FDA registered studies

- Only 51% positive
- 33 negative studies: 22 not published; 11 ***published conveying a positive outcome***
- Published literature: 94 % positive

Transparency Initiatives

- **ICMJE 2004** (JAMA, NEJM, Lancet, CMAJ…): trial registration and results reporting as condition publication
- **WHO International Clinical Trials Registry Platform 2006**: International standard- recommendation to register all clinical trials prior to recruitment subjects
- 2007 US FDA Amendment Act
- Various National Laws and Guidelines

European Medicines Agency

- Background: European Ombudsman Recommendation Re Paediatric Cancer Drugs & Access Requests by Cochrane Researchers
- EMA Policy/0043 Access to Documents 2010: Shift in Presumption
  - Before: Secrecy as Rule; Access to data to be justified by data requester
  - Now: Access = Rule; restriction = exception to be justified by industry
  - Release of 1,9 million pages data between 2011-2013
- Policy 2014 on prospective publication CT data: clinical data of regulated products to be publically available

Result Transparency Initiatives & Litigation

- Hundreds of thousands of pages of previously unavailable clinical trials data part of the public record
- Why reliance on litigation not sufficient?
  - Settlements with data secrecy
  - Access to justice & lack of class action litigation Europe
  - Only when beginning of knowledge of serious problems that affect many people or results in excessive spending

ANALYSIS

Restoring invisible and abandoned trials: a call for people to publish the findings

Unpublished and misreported studies make it difficult to determine the true value of a treatment. **Peter Doshi and colleagues** call for sponsors and investigators of abandoned studies to publish (or republish) and propose a system for independent publishing if sponsors fail to respond

Peter Doshi *postdoctoral fellow*[1], Kay Dickersin *professor, director*[2 3 4], David Healy *professor of psychiatry*[5], S Swaroop Vedula *postdoctoral fellow*[6], Tom Jefferson *researcher*[7]

First Restorative Publications

BMJ

Coding of adverse events of suicidality in clinical study reports of duloxetine for the treatment of major depressive disorder: descriptive study

OPEN ACCESS

Emma Maund *PhD student*[1], Britta Tendal *postdoctoral researcher*[1], Asbjørn Hróbjartsson *senior researcher*[1], Andreas Lundh *physician*[1 2], Peter C Gøtzsche *professor*[1]

[1]Nordic Cochrane Centre, Rigshospitalet Department 7811, Copenhagen, Denmark ; [2]Department of Infectious Diseases, Hvidovre University Hospital, Hvidovre, Denmark

Conclusion Data on adverse events in tables in clinical study reports may not accurately represent the underlying patient data because of the medical dictionaries and coding conventions used. In clinical study reports, the listings of adverse events for individual patients and narratives of adverse events can provide additional information, including original investigator reported adverse event terms, which can enable a more accurate estimate of harms.

Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications

Emma Maund *PhD student*[1], Britta Tendal *postdoctoral researcher*[1], Asbjørn Hróbjartsson *senior researcher*[1], Karsten Juhl Jørgensen *senior researcher*[1], Andreas Lundh *physician*[1 2], Jeppe Schroll *PhD student*[1], Peter C Gøtzsche *Professor*[1]

[1]Nordic Cochrane Centre, Rigshospitalet Dept 7811, Copenhagen, Denmark; [2]Department of Infectious Diseases, Hvidovre University Hospital, Kettegårds Allé 30, 2650 Hvidovre, Denmark

- **Conclusion** Clinical study reports contained extensive data on major harms that were unavailable in journal articles and in trial registry reports. There were inconsistencies between protocols and clinical study reports and within clinical study reports. Clinical study reports should be used as the data source for systematic reviews of drugs, but they should first be checked against protocols and within themselves for accuracy and consistency.

October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies

EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

LIPPINCOTT WILLIAMS & WILKINS

Journal of the American Academy of
CHILD & ADOLESCENT PSYCHIATRY

Volume 40(7) July 2001 pp 762-772

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

[Articles]

KELLER, MARTIN B. M.D.; RYAN, NEAL D. M.D.; STROBER, MICHAEL PH.D.; KLEIN, RACHEL G. PH.D.; KUTCHER, STAN P. M.D.; BIRMAHER, BORIS M.D.; HAGINO, OWEN R. M.D.; KOPLEWICZ, HAROLD M.D.; CARLSON, GABRIELLE A. M.D.; CLARKE, GREGORY N. PH.D.; EMSLIE, GRAHAM J. M.D.; FEINBERG, DAVID M.D.; GELLER, BARBARA M.D.; KUSUMAKAR, VIVEK M.D.; PAPATHEODOROU, GEORGE M.D.; SACK, WILLIAM H. M.D.; SWEENEY, MICHAEL PH.D.; WAGNER, KAREN DINEEN M.D., PH.D.; WELLER, ELIZABETH B. M.D.; WINTERS, NANCY C. M.D.; OAKES, ROSEMARY M.S.; MCCAFFERTY, JAMES P. B.S.

Alderman et al 1998 – “sertraline is **safe** and likely to be **effective** in pediatric patients.” (9%) Ambrosini, Wagner et al 1999 – “sertraline is **effective, safe and well tolerated**” (5.7%) Keller, Wagner et al 2001; Wagner et al 2002 Geller, Wagner et al 2002 – Wagner et al 2003 – “sertraline is an **effective and well tolerated** treatment for children and adolescents with MDD”

(analysis David Healy)

BMJ 2015: correction Keller et al.

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Joanna Le Noury,[1] John M Nardo,[2] David Healy,[1] Jon Jureidini,[3] Melissa Raven,[3] Catalin Tufanaru,[4] Elia Abi-Jaoude[5]

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[5]Department of Psychiatry, The Hospital for Sick Children,

ABSTRACT

OBJECTIVES

To reanalyse SmithKline Beecham's Study 329 (published by Keller and colleagues in 2001), the primary objective of which was to compare the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression. The reanalysis under the restoring invisible and abandoned trials (RIAT) initiative was done to see whether access to and reanalysis of a full dataset from a randomised controlled trial would have clinically relevant implications for evidence based medicine.

DESIGN

Double blind randomised placebo controlled trial.

(HAM-D score ≤8 or ≥50% reduction in baseline HAM-D) at acute endpoint. Prespecified secondary outcomes were changes from baseline to endpoint in depression items in K-SADS-L, clinical global impression, autonomous functioning checklist, self-perception profile, and sickness impact scale; predictors of response; and number of patients who relapse during the maintenance phase. Adverse experiences were to be compared primarily by using descriptive statistics. No coding dictionary was prespecified.

RESULTS

The efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any prespecified primary or secondary

UNIVERSITY OF
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University of Pennsylvania Perelman School of Medicine
Department of Psychiatry

September 23, 2016

Robert Freedman, MD
American Journal of Psychiatry
1000 Wilson Boulevard
Suite 1825
Arlington, Virginia 22209
ajp@psych.org

RE: Nemeroff CB, Evans DL, Gyulai L, Bowden CL, Gergel IP, Oakes R, Pitts CD. Double-Blind, Placebo-Controlled Comparison of Imipramine and Paroxetine in the Treatment of Bipolar Depression, American Journal of Psychiatry 2001; 158:906-912.

Dear Dr. Freedman:

We write to you as the editor in chief of the American Journal of Psychiatry to formally request immediate retraction of the Smith Kline Beecham, now GlaxoSmithKline (GSK), study report PAR 352 referenced above.

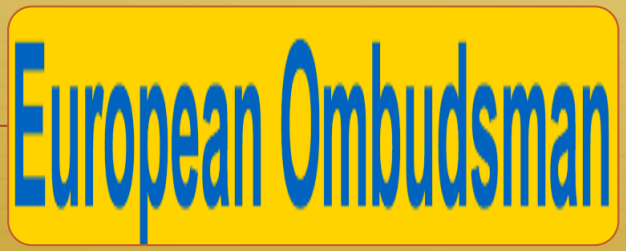
International Journal of Risk & Safety in Medicine 24 (2012) 221–231
DOI 10.3233/JRS-2012-0571
IOS Press

The paroxetine 352 bipolar trial: A study in medical ghostwriting

Jay D. Amsterdam[a,*] and Leemon B. McHenry[b]
[a]*Depression Research Unit, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[b]*Department of Philosophy, California State University, Northridge, CA, USA*

Meanwhile in the Courts…

Access Challenges European General Court

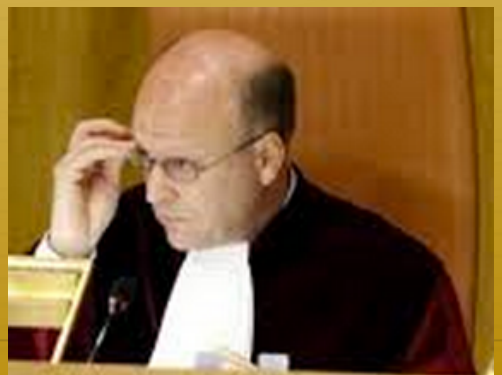


Interim Rulings EU GC AbbVie & Intermune Cases (May 2013)

Suspension data access decision: *prima facie* validity of claim that data access violates "right to the protection of professional secrets" (commercial secrecy nature of info) framed as fundamental "right to protection of private and family life" ECHR & European Charter

ECJ Appeal of Interim Decision (Dec. 2013)

- Vice-president ECJ annuls interim measure General Court: EMA can publish data Humira and Esbriet
  - Damages resulting from potential breach of commercial secrecy interest in data can be calculated ex post
  - Even if data would be protected as part of right to protection of private life, not all breaches of fundamental right have same consequences and are irreparable with financial damages



Result of litigation

- AbbVie withdraws lawsuit April/May 2014
- Response EMA; not immediately granting access; in fact: access very much on basis of ‘redaction’ request of AbbVie in lawsuit!
- Intermune: withdrew June 10, 2014
  - Data access?

Press release

29/09/2016

New judicial decisions at odds with EMA's efforts to allow access to documents on medicines

EMA appeals interim measures

The European Medicines Agency (EMA) has appealed two interim orders by the President of the General Court of the European Union (EU) to suspend the release of documents requested by third parties under Regulation (EC) no. 1049/2001, the so-called "Transparency Regulation". The first order blocked the release of a clinical study report for Translarna, a centrally authorised medicine for the treatment of Duchenne's muscular dystrophy, until a final ruling is given by the General Court. EMA was planning to provide access to the clinical study report in response to an access to documents request, with appropriate redactions in accordance with the Regulation.

The second order, issued at the same time, blocked the release of three toxicity studies

Human Rights and Access to Information: the Right to Health

- Right to obtain information and education related to health (e.g. abortion context)
- Right to ‘a system of health protection’ providing highest attainable level of health
- Claim: it should include SYSTEM OF RELIABLE and PUBLICLY ACCOUNTABLE KNOWLEDGE PRODUCTION and KNOWLEDGE DISTRIBUTION

Right of Access to Information

- Connected to Right of **Freedom of Expression** and Right to Health:
  - ECHR *The Sunday Times v. The United Kingdom* (1979)
    - Court mentions that particularly in matters of public health, the public has the right to be 'properly informed'
  - ECHR *Társaság a Szabadságjogokért v. Hungary* (1999)
  - IACHR: *Claude Reyes v. Chile 2006*: Government refusal to provide environmental impact assessment to representatives of public interest groups
    - "social control" enabled through access to information is essential for accountable government

Right to Protection of Private and Family Life (ECHR art. 8)

- *Guerra v Italy*, 1998: government's failure to provide "essential information" about the level of risks associated with living close to a chemical plant
- *Roche v United Kingdom*, 2005: failure of UK in its positive obligations to provide an effective and accessible procedure to enable individual risk assessment based on relevant information (mustard gas experiments on army personnel)

Right to Life (art. 2 ECHR)

- *Öneryildiz v. Turkey* ECHR 2004: obligation of government to inform people living next to garbage dump of risk of methane explosion

"the public's right to information … may also, in principle, be relied on for the protection of the right to life."

Right to Information-Component of Right to Health

- Connection to democratic governance: e.g. in freedom of speech cases (*Sunday Times*) & role of media & civil society as 'public watchdog' (*Társaság a Szabadságjogokért v. Hungary*; IACHR: *Claude Reyes et al. v. Chile* 2006)
- Right to information as a component of Public Accountability of companies and regulator

Obligation to Produce Information

"[...] the generation of information suitably disaggregated to identify these disadvantaged sectors or groups deprived of the enjoyment of rights is not only a means to ensure the effectiveness of a public policy, but a core obligation that the State must perform *in order to fulfill its duty to provide special and priority assistance to these sectors.*"

Organization of the American States [OAE], Inter-American Commission of Human Rights [IACHR], Guidelines for Preparation of Progress Indicators in the Area of Economic, Social, and Cultural Rights, OAS Official Records Series. OEA/Ser.L/V/II, para. 58.

Obligation to produce info

- Art. 31 **UN Convention on the Right of People with Disabilities**: obligation to collect and disseminate information (statistical and research data) that enables the State to formulate and apply public policies for the protection of the rights enshrined in the Convention (the right to health or the right to education, …)

- Art. 8 Convention (Belem do Paro) on Prevention, Punishment & Eradication of Violence against Women: 8(h) States have to take progressive steps to "ensure research and gathering of statistics and other relevant information" for monitoring violence against women and evaluating the effectiveness of State policies on the protection of the rights of women enshrined in the Convention.

Importance of Right to Information – Right to Health

- Interpretative shield against arguments pro secrecy of data based on commercial interests
- Recognition of obligation of states to implement reliable system of knowledge production
- Right to Information: Recognition of role of civil society in democratic governance (*Claude Reyes v. Chile* case)

What kind of legal intervention do we need?

- Strict application of types of legal rules we already have: criminal law where appropriate
- Fraud provisions
- Regulatory and professional sanction towards investigators/ CROs/pharmacuetical companies
- **Global Coordination of rules needed: e.g.** access to data and sharing of results grounded in international IP and Human Rights principles
- Clear legal rules about commercial secrecy and access to data

More Radical Reform

- W. Ray & M. Stein, "Reform of Drug Regulation—Beyond an Independent Drug-Safety Board" 2006 *NEJM* 194-201 (354(2): New Independent Drug Agency, funded by tax on pharmaceuticals:
  - *Center for Drug Approval*
  - *Center for Post-Marketing Studies*
  - *Center for Drug Information*
- Need for Independent Drug Testing Agency to separate those with financial interests in outcome of research from those who design, conduct, analyze and publicize results

Further Info

T. Lemmens & C. Telfer, "Access to Data and the Right to Health: The Human Rights Case for Clinical Trials Transparency" (2012) 31(1) *Am. J. L. & Med.* 63-112 & **"Pharmaceutical Knowledge Governance: A Human Rights Perspective"** (2013) (41)(1) *J.L. Med. Ethics* 163

"EMA's Proposed Data Release Policy: Promoting Transparency or Expanding Pharma Control over Data?" (blog) *PLoS Speaking of Medicine*, May 30, 2014

S. Gibson & T. Lemmens, "Niche Markets and Evidence Assessment in Transition : A Critical Review of Proposed Drug Regulatory Reforms" (2014) 22(2) *Medical Law Review* 200-220

T. Lemmens & S. Gibson, "Decreasing the Data Deficit: Improving Post-Market Surveillance in Pharmaceutical Regulation" (2014) 59(4) *McGill Law Journal* 943-988