

Conflicts of interest in regulation and the meaning of 'effectiveness' and 'safety'

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Mad Medicine, Cork, Sept 24, 2011



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“A conflict of interest is a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.”

- US Institute of Medicine, April 2009



“The relationship between a regulator and the regulated... must never become one in which the regulator loses sight of the principle that it regulates only in the public interest and not in the interest of the regulated.”

- Justice Krever, Commission of Inquiry on the Blood System in Canada, 1996





Historical aim of regulation: prevent repeat drug disasters

- Elixir sulfanilamide, USA 1938
- Thalidomide, 1959-1961
- DES (diethylstilbestrol), 1948-1970's
- Vioxx (rofecoxib), 1999-2004
- Mediator (benfluorex), 2009



DES (diethylstilbestrol): US FDA's first “controversial test case”

- FDA set up in 1938
- Approval refused in 1940
- Companies could reapply
- “Clinical trials” and intense lobbying
- 1941 compromise: approved, but contraindicated in pregnancy
- 1947 approved in pregnancy



1957

"Really?"



Yes ...

desPLEX[®]

to prevent **ABORTION, MISCARRIAGE** and
PREMATURE LABOR

*recommended for routine prophylaxis
in ALL pregnancies . . .*

96 per cent live delivery with **desPLEX**
in one series of 1200 patients⁴—
— bigger and stronger babies, too.^{1, 5}

No gastric or other side effects with **desPLEX**
— in either high or low dosage^{3, 4, 5}

(Each **desPLEX** tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating to assure prompt help in emergencies. **desPLEX** tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

For further data and a generous
trial supply of **desPLEX**, write to:
Medical Director

REFERENCES

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GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.

«... I think I always accepted the fact that one was going to get bullied and pressured by industry. It was understandable that the companies were very anxious to get their drugs approved. »

-Frances Kelsey, thalidomide reviewer

-http://www.fda.gov/fdac/features/2001/201_kelsey.htm





Regulatory agency “structurally and culturally in a position of conflict of interest”
- IGAS (*Inspectorate General of Social Affairs*), Jan 2011



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Servier charged with deception and fraud

Le Monde, Sept 21, 2011



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European Medicines Agency

“..no proper guarantee of the independence of experts hired to carry out scientific evaluations of human medicines and some experts had conflicting interests...”

- April 2011, European Parliamentary Committee on Budgetary control



Science

+



Judgment

Regulatory
decisions



Regulation post-thalidomide

1. Laboratory and animal studies

2. Pre-market clinical trials

- Phase I – healthy volunteers
- Phase II – small-scale, dose-ranging
- Phase III – 2 to 3 randomized controlled trials

3. Post-market surveillance

- Adverse drug reaction reporting
- Periodic safety update reports
- Pharmaco-epidemiological studies

Sources of conflicts of interest

- Industry financing of regulation
- Speed versus quality
- Clinical trial design
- Conflicted expert advisors
- International harmonization
- Secrecy
- The revolving door



Industry licensing fees

“This arrangement... tends to put the drug companies in the position of clients of the IMB [*Irish Medicines Board*] with the inference that the IMB has a corresponding obligation to meet its ‘clients’ needs. This is not an ideal position for an agency concerned with public safety.”

- Houses of the Oireachtas, Joint Committee on Health and Children, Dublin, 2007



Drug-review deadlines and safety problems

-Carpenter et al NEJM 2008; 358: 1354-61

- Drugs approved in 2 months pre-deadline
 - Safety withdrawals 5 times as likely
 - Warning of serious risks 4 times as likely



Selective publication of trials and results



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Pre-market antidepressants studies

- *Turner et al. N Engl J Med 2008;358:252-60*

74 clinical trials

- Drug better than placebo in 38
 - 37 published
- 12 with questionable results
 - all published; 6 with spin
- In, 24 drug no better than placebo
 - 8 published; 5 with spin

Expand use beyond benefit



CRESTOR IS INDICATED FOR THE PREVENTION OF MAJOR CARDIOVASCULAR EVENTS*

In adult patients without documented history of cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease, CRESTOR is indicated to:

- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of nonfatal stroke
- Reduce the risk of nonfatal atherosclerotic cardiovascular disease

CRESTOR is also indicated as an adjunct to diet, or (when appropriate) to the adult Treatment Panel B (ATP II) statin, for the reduction of elevated total cholesterol (TC), LDL-C, ApoB, the total CVD risk score and triglycerides (TG) and for increasing HDL-C in hyperlipidemic and dyslipidemic conditions, when response to diet and/or statin alone has been inadequate, including primary hypercholesterolemia (Type IIa including heterozygous familial hypercholesterolemia and some nonfamilial hypercholesterolemia), combined (mixed) dyslipidemia (Type IIb), or homozygous familial hypercholesterolemia where CRESTOR is used either alone or as an adjunct to diet and other lipid-lowering treatment such as ezetimibe.

In the IMPROVE-IT trial, there were no statistically significant treatment differences between the CRESTOR and placebo groups for death due to cardiovascular causes or hospitalizations for probable angina.

The majority of patients are controlled at the 20 mg dose.

In pregnancy, a dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events. CRESTOR is contraindicated in patients who are hypersensitive to any component of the medication, in patients with active liver disease or asymptomatic persistent elevation of serum transaminases exceeding 3 times the upper limit of normal, in pregnant and nursing mothers and in patients using concomitant cyclosporin. CRESTOR 40 mg is contraindicated in patients with predisposing factors for myopathy/ rhabdomyolysis and in Asian patients.

Rare cases of myopathy with acute renal failure secondary to myoglobinuria have been reported with CRESTOR and with other HMG-CoA reductase inhibitors.

CRESTOR, as well as other HMG-CoA reductase inhibitors, should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Patients who develop a dry eye or eye pain as suggestive of eye pathology should have their CC levels adjusted. CRESTOR therapy should be discontinued if markedly elevated CK levels (≥ 10 x ULN) are observed or myopathy, diagnosed or suspected.

In the IMPROVE-IT trial, CRESTOR 20 mg was observed to increase plasma glucose levels, which were reflected in shift in the proportion of subjects in the diabetes mellitus states.

Most commonly reported adverse events in hypercholesterolemia vs. placebo were headache (1.4% vs. 2.2%), abdominal pain (1.7% vs. 2.2%), flatulence (1.8% vs. 2.7%) and nausea (2.2% vs. 3.0%).

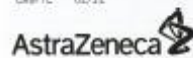
Most commonly reported adverse events in prevention of major cardiovascular events vs. placebo were urinary tract infection (1.7% vs. 5.0%), nasopharyngitis (2.0% vs. 2.2%), back pain (1.6% vs. 3.5%) and myalgia (1.0% vs. 3.0%).

See the Product Information graph for full contraindications, warnings, precautions, dosing and administration.

Reference: 1. CRESTOR IP Product Monograph, AstraZeneca Canada Inc. 8 October 2014.

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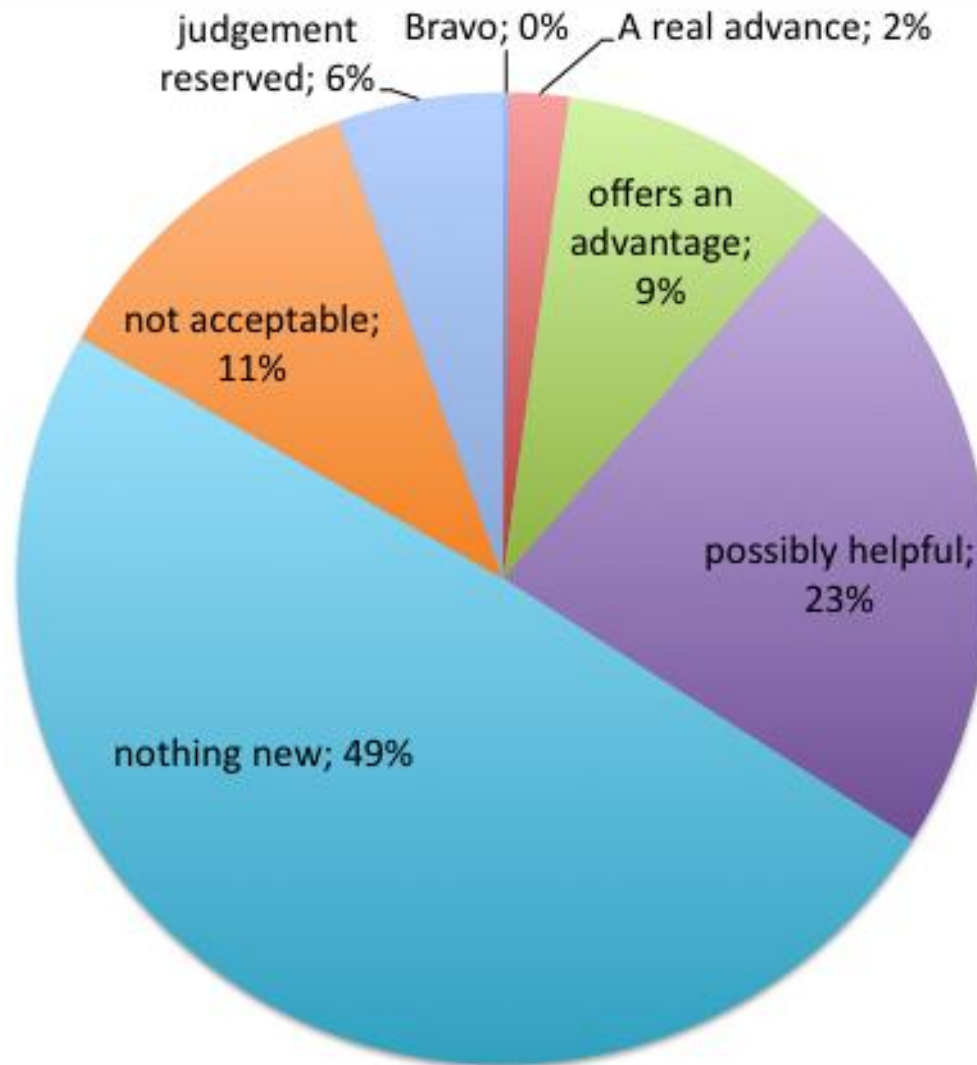
See prescribing summary on page 838

How to get the clinical trial results you want

- Placebo run-in: exclude responders
- Drug run-in: include only responders
- Drug run-in: randomize patients to withdrawal
- Short term studies, surrogate outcomes
- Exclude older, sicker patients
- Report on only a subset of participants
- Non-inferiority trials
- Wrong comparator / wrong dose



Ratings of 961 new drugs and indications in France, 1999 to 2008 – *La Revue Prescrire*



US FDA expert advisory committees

- *Lurie et al. JAMA. 2006;295:1921-8*

- 73% of 221 meetings had conflicted members or voting consultants
- 28% of all advisors had conflicts
- 47 “public speakers” were flown in by sponsors to speak at these meetings



Who is asked to provide advice? A Canadian example

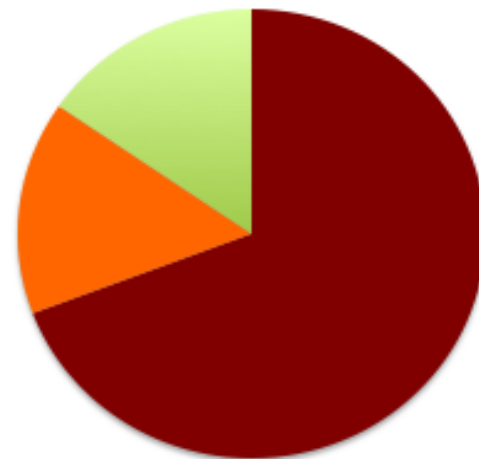
« The Schedule A Working Group was comprised of invited representatives from professional associations, consumer and advocacy groups, advertising, media, foods, health products and medical devices and Health Canada, **with a balanced representation from professional, industry and consumer groups.**»

http://www.hc-sc.gc.ca/hpfb-dgpsa/sched_a_intro_letter_e.html



Who was there?

- **Food industry representative**
- **Natural health products**
- **Over-the-counter drugs**
- **Functional foods/ nutraceuticals**
- **Advertising and media association**
- **Canadian Pharmacists Association (OTC consultant)**
- **Best Medicines Coalition (brand-name industry \$\$)**
- **Canadian Dermatology Association (sunscreen \$\$)**
- **Naturopaths association (office sales of natural \$\$)**
- **Complementary medicines researcher (\$\$?)**
- **Canadian Medical Association**
- **Union des Consommateurs (independent; dissenting report)**
- **Women and Health Protection (independent; dissenting report)**
- **Co-Chair: Claire Bombardier, lead author, VIGOR trial**



What is safe enough or effective enough? A few questionable examples



British Medical Journal



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“Are you suggesting it was political?” Zanamivir (Relenza) for flu

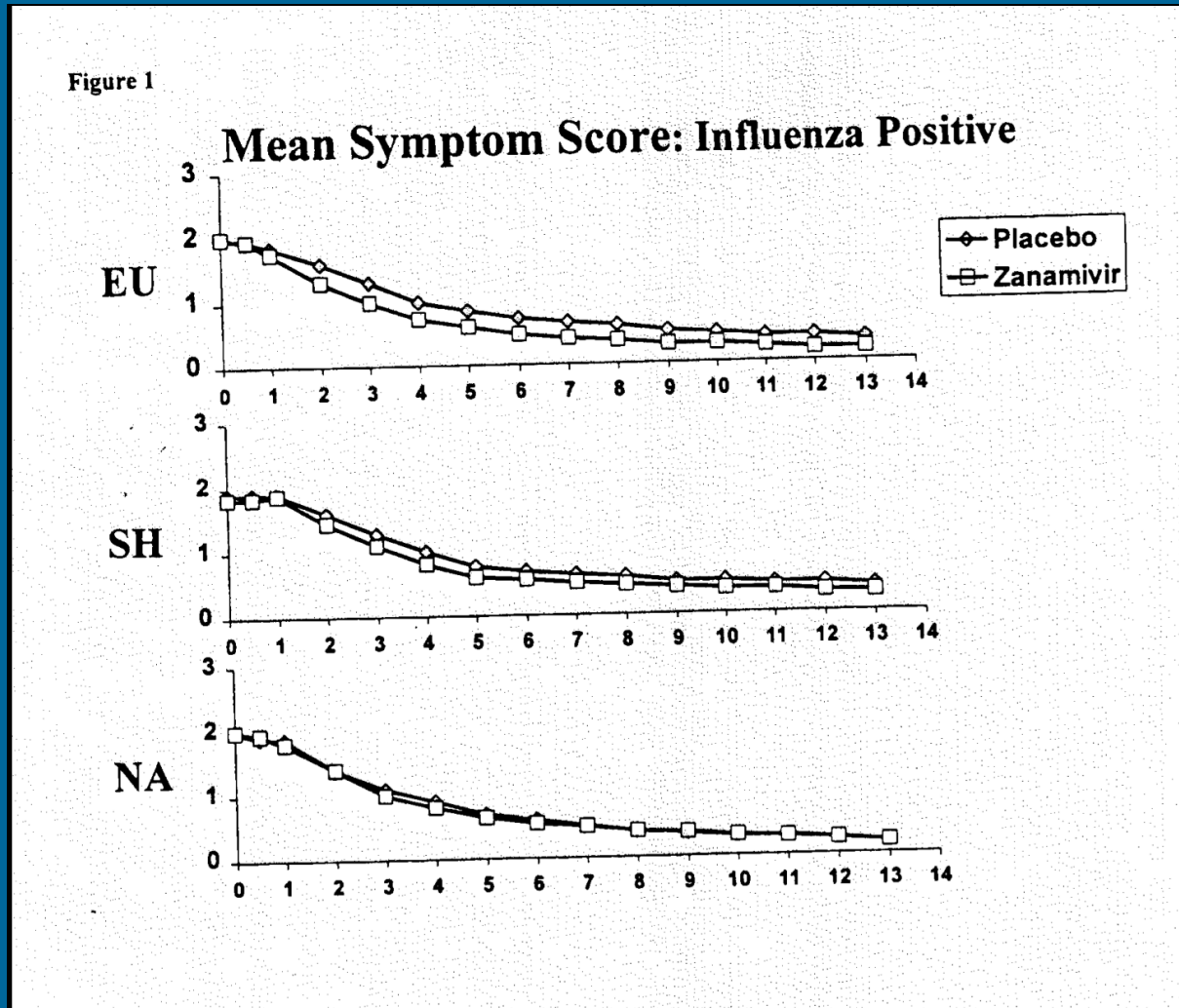


Figure 1: FDA Statistical review; days 0-14 of treatment.
0= no symptoms; 3= severe



1-866-YAZ-PMDD

www.YAZ-us.com

FDA Warning letter – Yaz Oct 2008
“The TV ads are misleading because they broaden the drug’s indication, overstate the efficacy of YAZ and minimize serious risks...”

50 years post thalidomide, how to re-prioritize public health?

- Address the problems with governance
 - Financing via tax revenues
 - Full access to information
 - Enable citizens to be engaged
 - Eliminate conflicts of interest
- Address the problems with the science
 - Ensure health benefits outweigh harm
 - Require comparative advantage
 - Public conduct of trials
- Replace the “permissive principle” with a precautionary approach

Thank you!



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