THE GHOSTMANAGEMENT OF MEDICAL RESEARCH:

The emergence of corporate science

Presentation for
Carleton University, Ottawa

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OUTLINE

Part 1: The political economy of Big Pharma

Part 2: Promotion as core activity: Manufacturing influence.

Part 3: The Ghostmanagement of medical research.

Part 1:

Overview of the political economy of the pharmaceutical sector

Some indicators

- In 2009, the global market for pharmaceuticals was around US$808 billion, representing 3.8% of the world's industrial production. (According to IMS Health)

- From 2000 to 2009, the average annual increase in world GDP was 3.6%, while average annual pharmaceutical sales grew by 8.5%. (10.5% in Canada).

Big Pharma = 80% of world market share

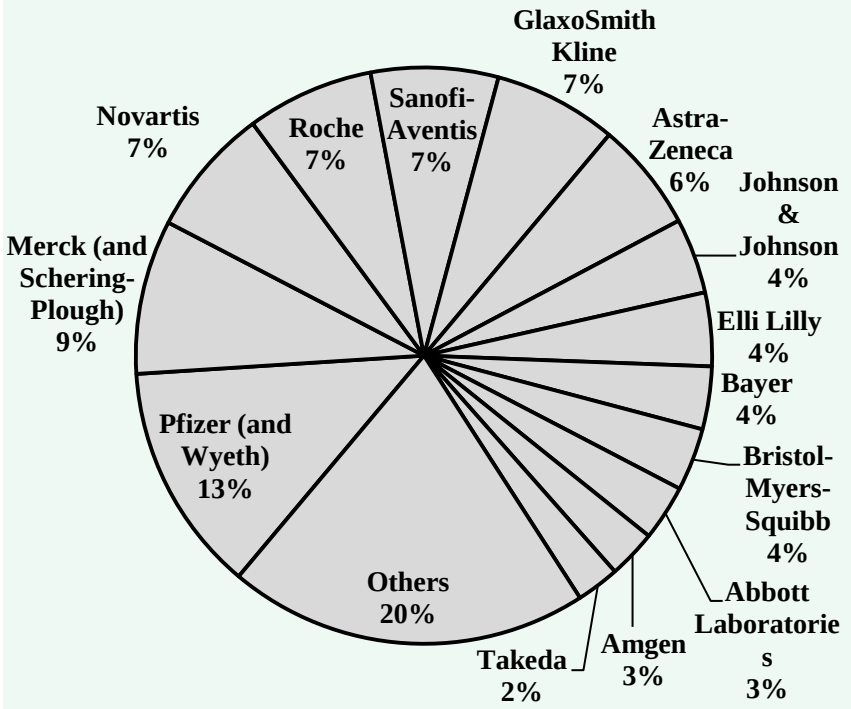
List of Big Pharma Companies, Sept. 30 2008

Company	Country	FT Global 500 Rank	Market Value (Billion $)
1- Johnson and Johnson	US	10	193.6
2- Novartis	Switzerland	25	138
3- Roche	Switzerland	26	134.3
4- Pfizer	US	31	124.3
5- GlaxoSmithKline	UK	38	112.6
6- Genentech	US	53	93.6
7- Abbott Laboratories	US	58	88.8
8- Sanofi-Aventis	France	59	86
9- Merck	US	77	67.6
10- AstraZeneca	UK	83	63.5
11- Amgen	US	85	62.7
12- Bayer	Germany	106	55.6
13- Eli Lilly	US	111	50.1
14- Wyeth	US	115	49.3
15- Bristol-Myers-Squibb	US	150	41.3
16- Takeda Pharmaceutical	Japan	155	40.3
17- Schering Plough	US	220	30
Total	-	-	**1431.6**

Source: FT Global 500, Fortune Global 500

Mergers and Acquisitions

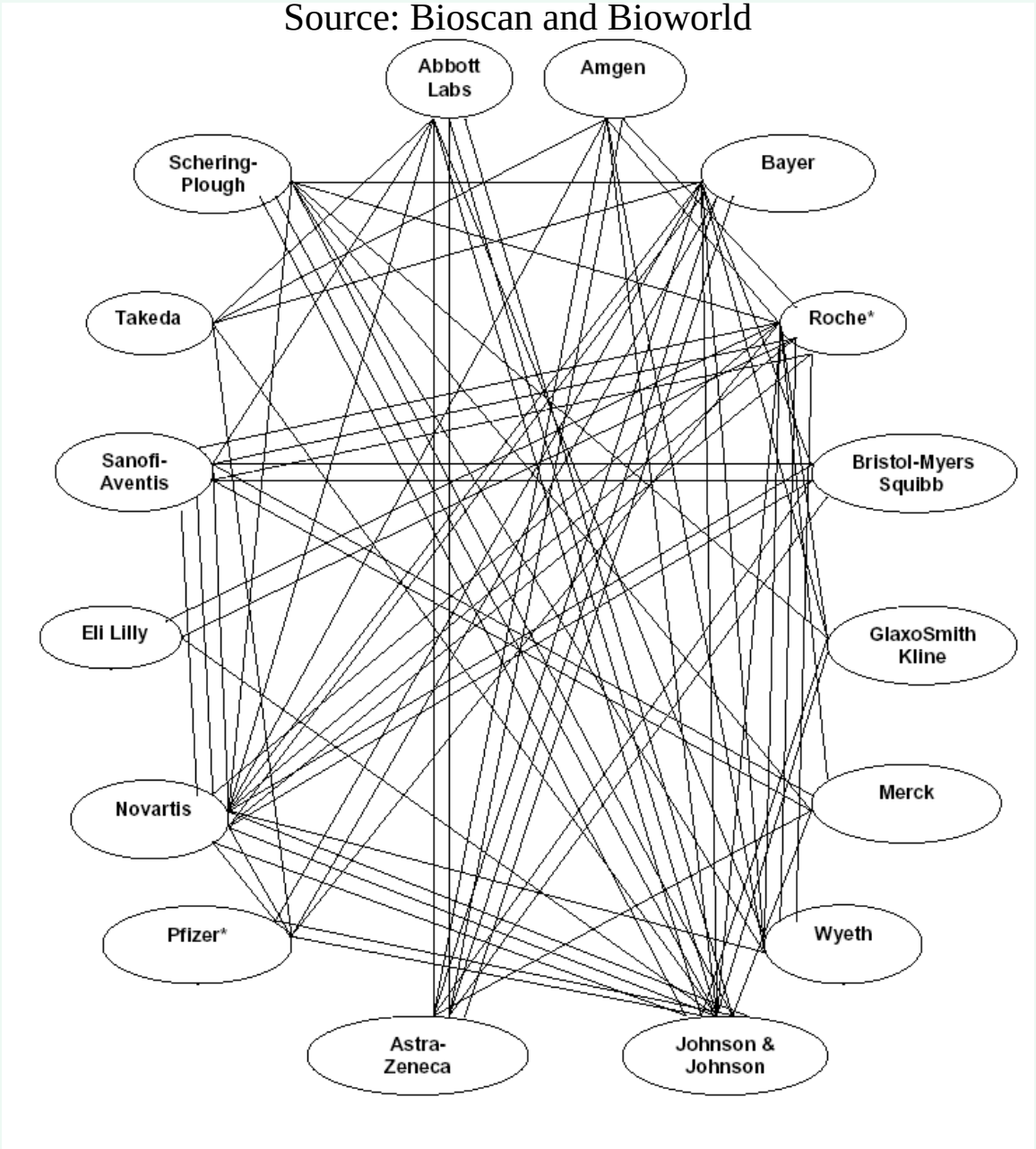
Drug Sales as a Share of Total Market, 2009



Sources: Cowen and Co. (Investext), Takeda and Bayer corporate websites

On-Going Cooperation Agreements Among Big Pharma, May 2008

Source: Bioscan and Bioworld

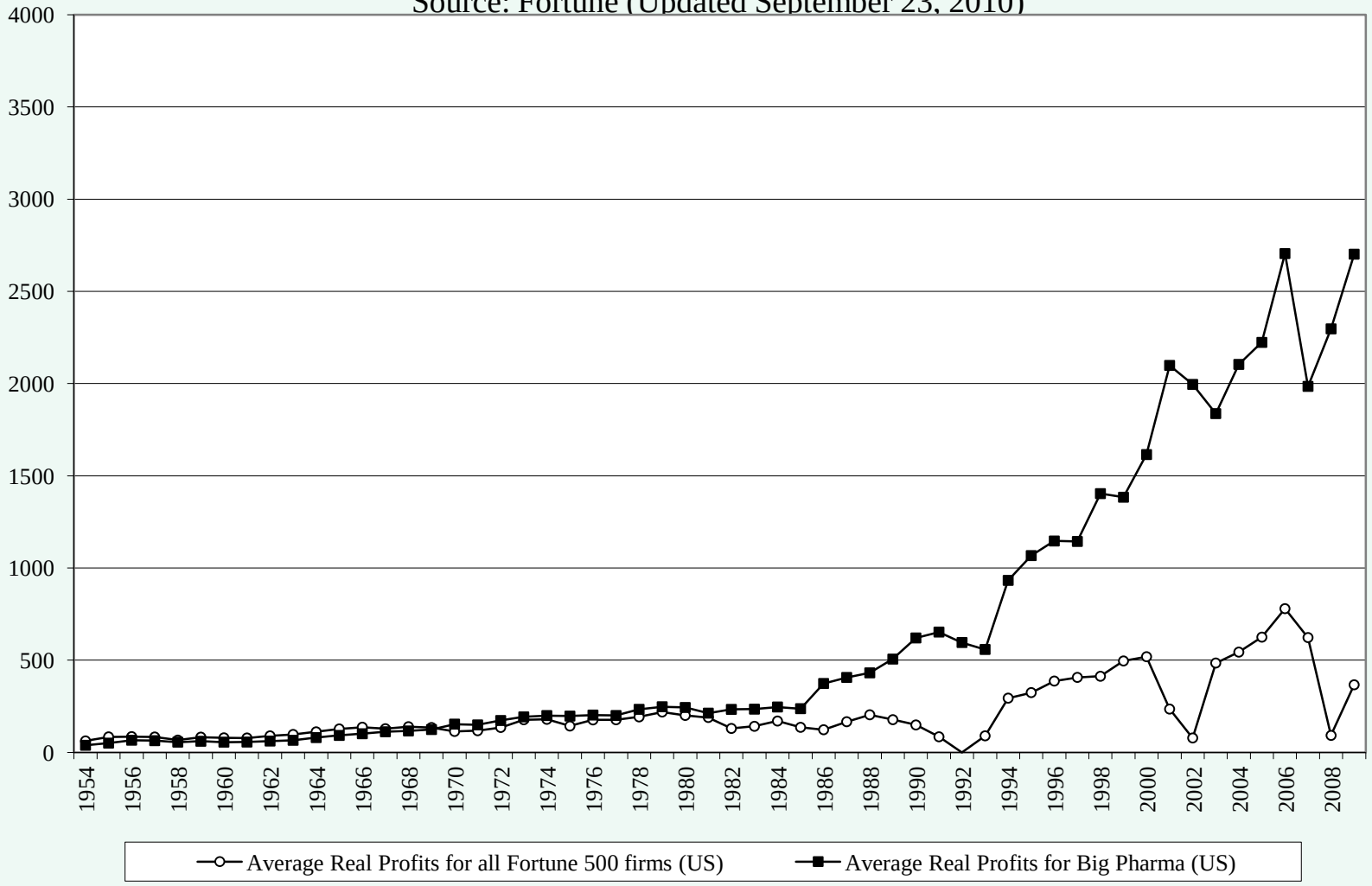


Big Pharma Differential Accumulation;

Average real profits of US dominant pharmaceutical firms as compared to average real profit of Fortune 500 firms

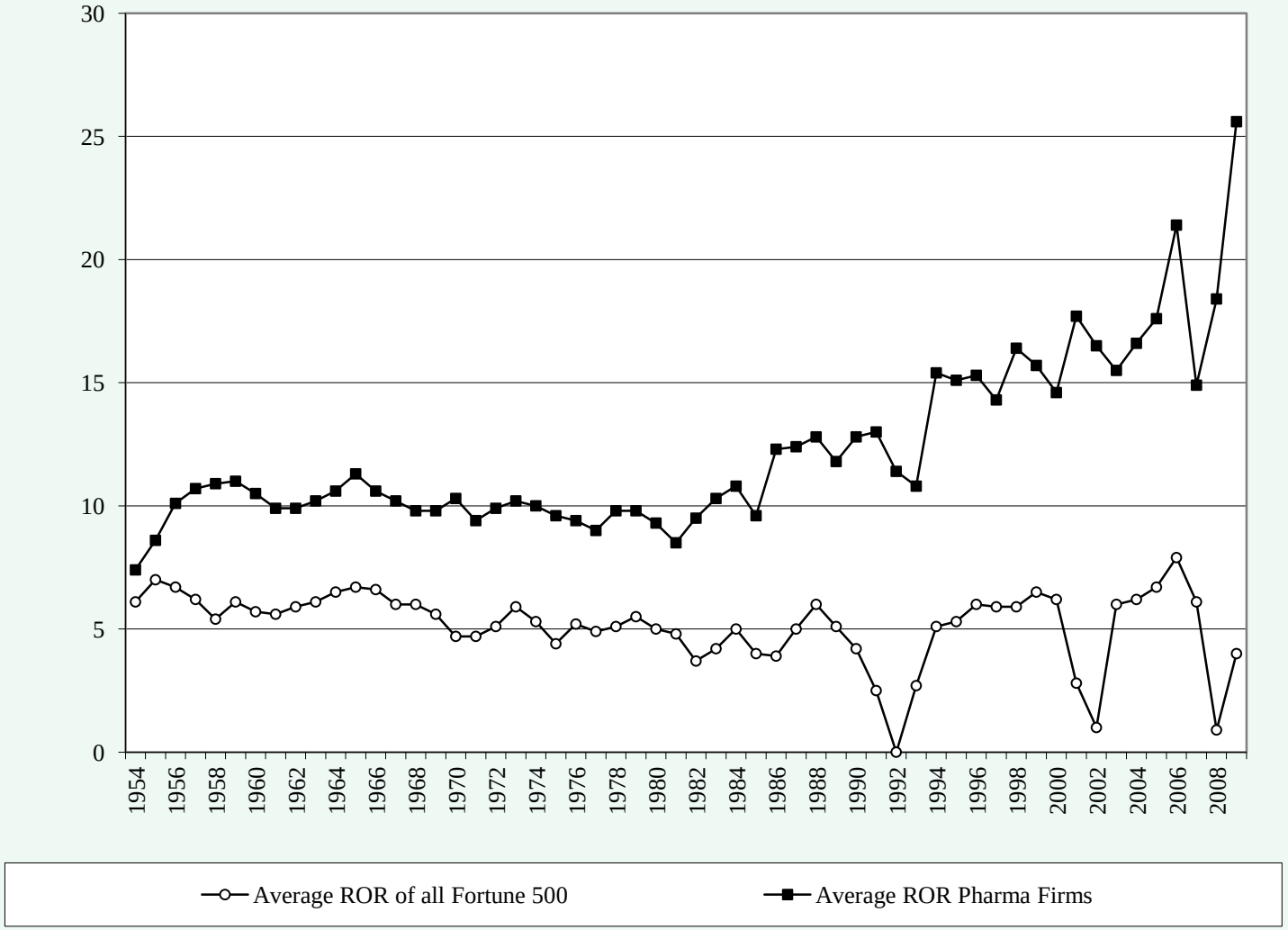
(1954-2009; in millions of constant 1984 US$)

Source: Fortune (Updated September 23, 2010)



Differential Returns on Revenues (ROR) Between Big Pharma and Fortune 500 (Profits per unit sold) 1954-2009

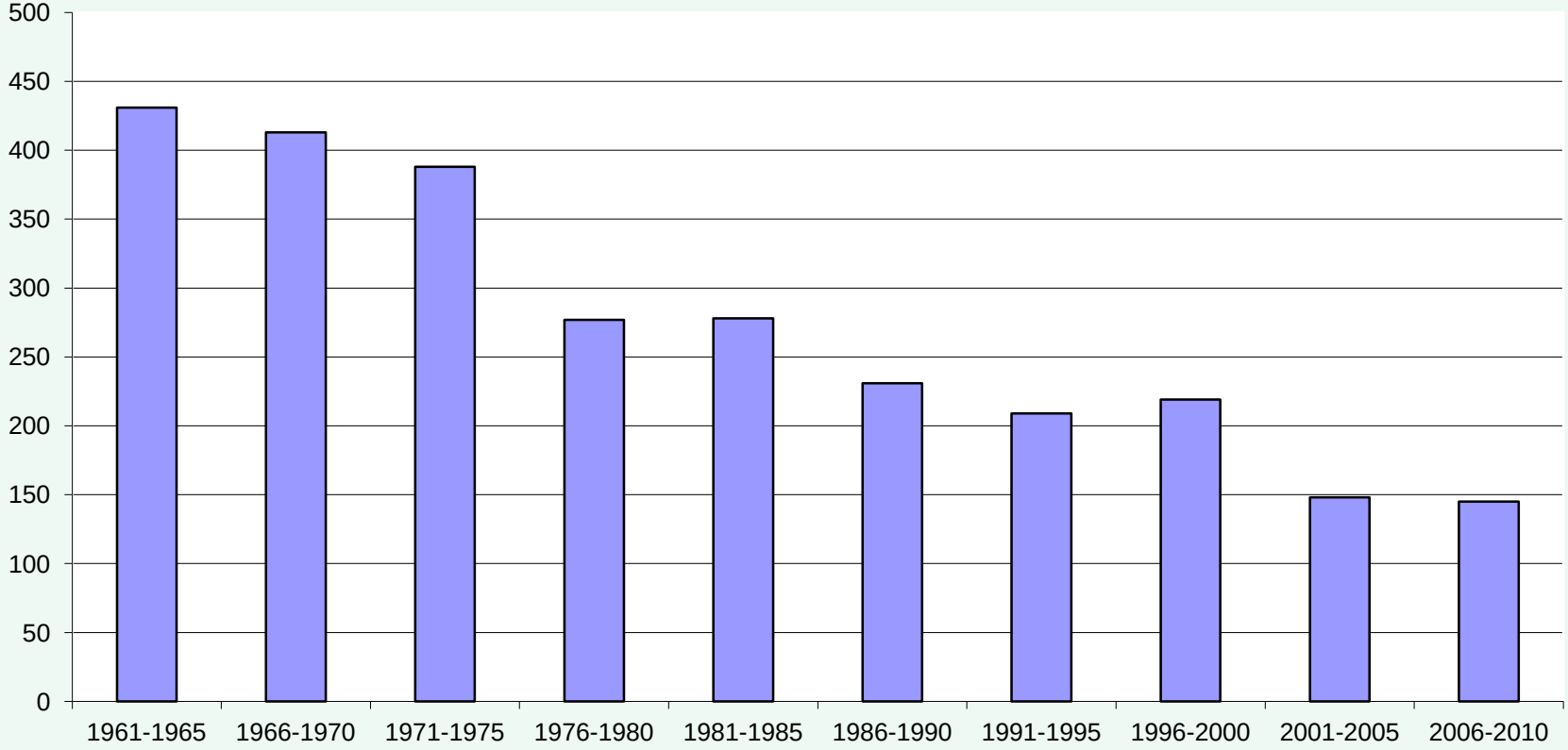
Source: Fortune Magazine (Updated September 23, 2010)



The Innovation Crisis

A Quantitative Analysis

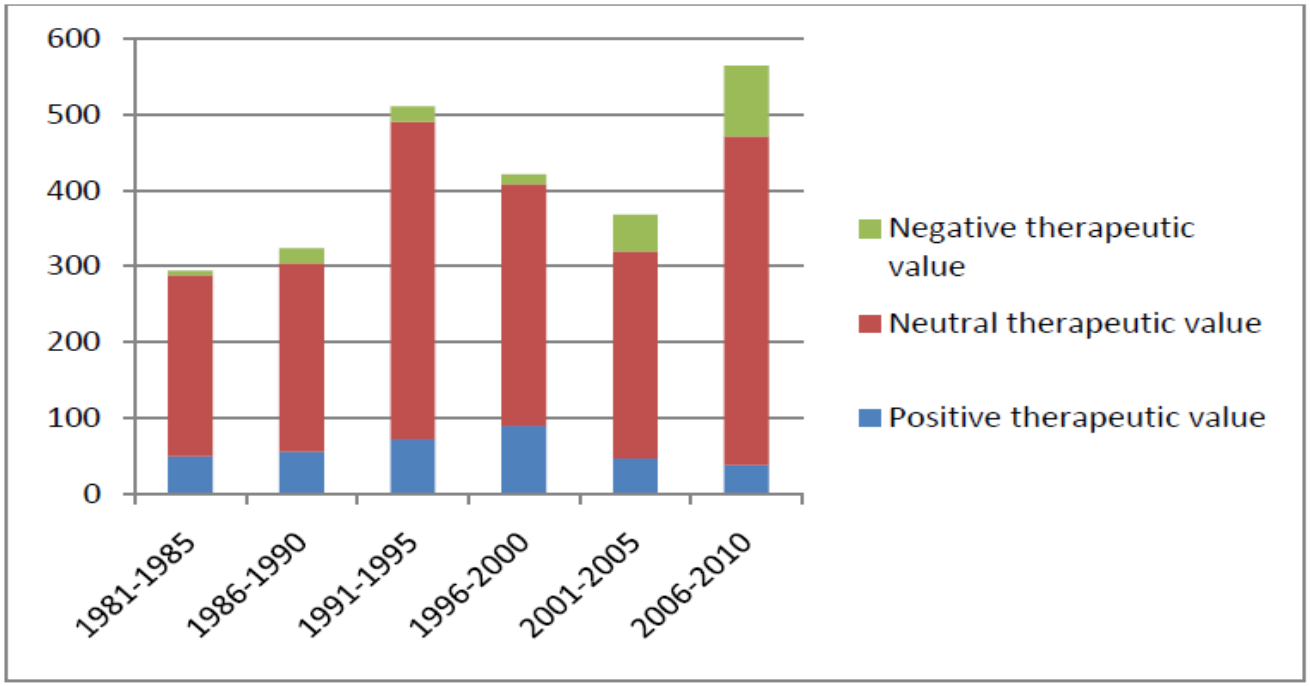
Introductions of New Molecular Entities 1961-2010*



Sources: 1961-1985: Erika Reis-Arndt (quoted in Redwood 1987). Data includes only new chemical entities.
1986-1999: IMS Lifecycle New Product Focus Database (quoted in Grabowski and Wang 2006). Data includes all NMEs (including biologics).
2000-2009: SCRIP (quoted in EFPIA, various years). Data includes all new active substances (including NMEs and radiopharmaceuticals) .
*: The number of new active substances for 2010 has been calculated as the average of new active substances introduced between 2006 and 2009.

The Innovation Crisis

Percentage of Marketed New Drugs Representing a Therapeutic Advance in the French Pharmacopoeia between 1981 and 2009 according to *Prescrire*



Sources: Prescrire (#213 p.59; #224 p.56, #280 p.142; #304 p.139; #316 p.139).

- In 2012, 82 new drugs were introduced in France.
- 4 (5%) were considered to bring a therapeutic advance (1 major, 3 minor).
- 56 (68%) did not bring anything new to the existing pharmacopoeia
-15 (18%) were harshly criticized because they were commercialized while having a negative risk-benefit ratio.
-Not clear if we have an improvement or regression of the pharmacopoeia.

Part 2:

Pharmaceutical promotion as a core activity:
Producing influence.

Promotion and the Price of Drugs

The doctor is a medication purchaser without any budgetary constraint. The physician often has no idea about the price charged for the products he prescribes. This lack of budgetary constraint is unique to the pharmaceutical sector.

Demand without Budgetary Constraint

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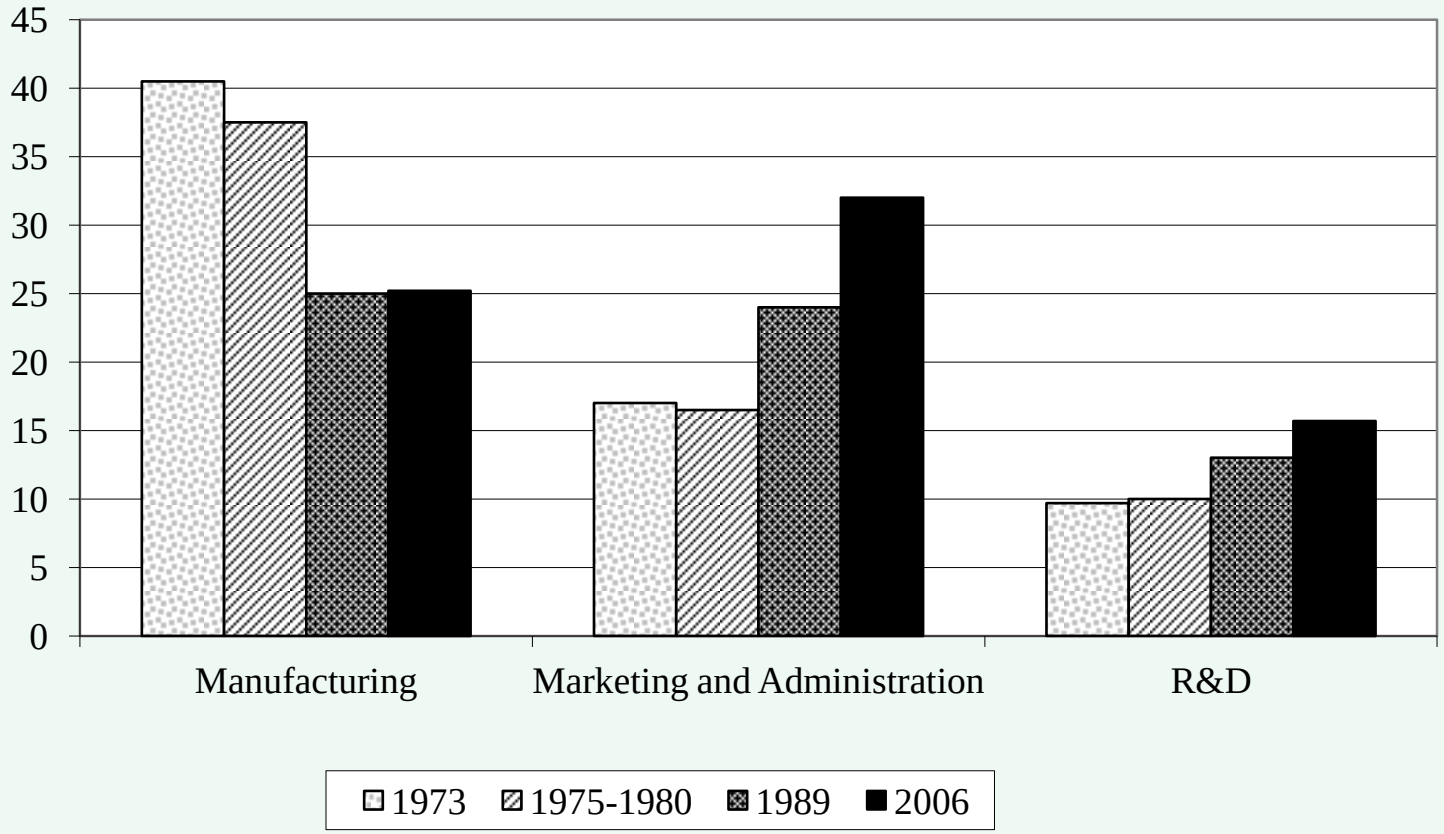
El Dorado of Economic Theory

Changing Cost Structure in Core Pharmaceutical Companies

(1973, 1975-1980, 1989 & 2006; % of sales)



Source: Ballance et al. (1992), Firms' Annual Reports 2006

Promotional Expenditures in Pharmaceuticals in the United States in 2004: A New Estimate

Marc-André Gagnon and Joel Lexchin, "The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States", *PLoS Medicine*, vol. 5, #1, January 2008: pp.1-6.

Table 7.3: A New Estimate: Pharmaceutical Promotional Spending in the United States in 2004

Type of Promotion	Billion $	% of Total
Retail Value of Samples (IMS)	15.9	27.7%
Sales Rep Contacts (CAM)	20.4	35.5%
DTCA (CMR)	4	7%
Meetings (CAM)	2	3.5%
E-Promotion, mailing, clinical trials (CAM)	0.3	0.5%
Journal Advertising (IMS and CAM)	0.5	0.9%
Undisclosed marketing (CAM)	14.4	25%
Total	**57.5**	**100%**

Source: IMS, CAM, CMR

Promotional Expenditures in Pharmaceuticals in the United States in 2004: A New Estimate

<u>Understanding the proportions</u>:

Sales: $239.8 billion

R&D: $24.1 billion (10% of revenues)

Promotion: $57.5 billion (24.4% of revenues)

Promotion directed towards physicians: $42.8 billion

Number of Practicing physicians: 700 000

Average promotion spending per physician: $61,000

1 drug rep for every 6 physicians

Other undisclosed types of promotion: Fellowships, ghost writing, « off-label » promotion, seeding trials

Physician Category	Technique	How It Sells Drugs	Comments
Friendly and outgoing	I frame everything as a gesture of friendship. I give them free samples not because it's my job, but because I like them so much. I provide office lunches because visiting them is such a pleasant relief from all the other docs. My drugs rarely get mentioned by me during our dinners.	Just being friends with most of my docs seemed to have some natural basic effect on their prescribing habits. When the time is ripe, I lean on my "friendship" to leverage more patients to my drugs...say, because it'll help me meet quota or it will impress my manager, or it's crucial for my career.	Outgoing, friendly physicians are every rep's favorite because cultivating friendship is a mutual aim. While this may be genuine behavior on the doctor's side, it is usually calculated on the part of the rep.
Aloof and skeptical	I visit the office with journal articles that specifically counter the doctor's perceptions of the shortcoming of my drug. Armed with the articles and having hopefully scheduled a 20 minute appointment (so the doc can't escape), I play dumb and have the doc explain to me the significance of my article.	The only thing that remains is for me to be just aggressive enough to ask the doc to try my drug in situations that wouldn't have been considered before, based on the physician's own explanation.	Humility is a common approach to physicians who pride themselves on practicing evidence-based medicine. These docs are tough to persuade but not impossible. Typically, attempts at geniality are only marginally effective.
Mercenary	The best mercenary docs are typically found further down the prescribing power scale. There are plenty of 6's, 7's, and 8's [lower prescribing doctors] who are eagerly mercenary but simply don't have the attention they desire fawned on them. I pick a handful out and make them feel special enough with an eye towards the projected demand on my limited resources in mind. Basically, the common motif to docs whom you want to "buy out" is to closely associate your resource expenditure with an expectation—e.g., "So, doc, you'll choose Drug X for the next 5 patients who are depressed and with low energy? Oh, and don't forget dinner at Nobu next month. I'd love to meet your wife."	This is the closest drug-repping comes to a commercial exchange. Delivering such closely associated messages crudely would be deemed insulting for most docs so a rep really has to feel comfortable about their mercenary nature and have a natural tone when making such suggestions.	Drug reps usually feel more camaraderie with competing reps than they do with their clients. Thus, when a doctor fails to fulfill their end of the prescriptions-for-dinners bargain, news gets aroun and other reps are less likely to invest resources in them.
High-prescribers	I rely on making a strong personal connection to those docs, something to make me stand out from the crowd.	Friendship sells. The highest prescribers (9's and 10's) are every reps sugar mommies and daddies. It's the equivalent of spitting in the ocean to try to buy these docs out because, chances are, every other rep is falling head over heels to do so.	The highest prescribers receive better presents. Some reps said their 10's might receive unrestricte "educational" grants so loosely restricted that they were the equivalent of a cash gift, although I did not personally provide any grants.
Prefers a competing drug	The first thing I want to understand is why they're using another drug as opposed to mine. If it's a question of attention, then I commit myself to lavishing them with it until they're bought. If they are convinced that the competitor drug works better in some patient populations, I frame my drug to either capture another market niche or, if I feel my drug would fare well in a comparison, I hammer its superiority over the competing drug.	If, during the course of conversations, the doctors say something that may contradict their limited usage of our products, then the reps will badger them to justify that contradiction. This quickly transforms the rep from a welcomed reprieve to a nuisance, which can be useful in limited circumstances. We force the doctors to constantly explain their prescribing rationale, which is tiresome. Our intent is to engage in discourse but also to wear down the doc until he or she simply agrees to try the product for specific instances (we almost always argue for a specific patient profile for our drugs).	For reps this is a core function of our job. We're trained to do this in as benign a way as possible. No doc likes to be told their judgment is wrong so the latter method typically requires some discretion.
Acquiescent docs	Most docs think that if they simply agree with what the rep says, they'll outsmart the rep by avoiding any conflict or commitment, getting the samples and gifts they want, and finishing the encounter quickly. Nothing could be further from the truth. The old adage is true, especially in pharmaceutical sales: there is no such thing as a free lunch.	From the outset of my training, I've been taught to frame every conversation to ultimately derive commitments from my clients. With every acquiescent nod to statements of my drug's superiority I build the case for them to increase their usage of my product. They may offer me false promises but I'll know when they're lying: the prescribing data is sufficiently detailed in my computer to confirm their behavior. Doctors who fail to honor their commitments, no matter how casually made, convert the rep into a badgering nuisance. The docs are often corralled into a conversational corner where they have to justify their previous acquiescence.	Gifts are used to enhance guilt and social pressure. Reps know that gifts create a subconscious obligation to reciprocate. New reps who doubt this phenomenon need only see their doctors' prescribing data trending upwards to be convinced. Of course, most of these doctors think themselves immune to such influence. This is an illusion reps try to maintain.
No-see/ No-time (hard-to-see docs)	Occasionally docs refuse to see reps. Some do it for ethical reasons, but most simply lack the time. Even when I don't manage to see the doctor, I can still make a successful call by detailing the staff. Although they're on the doc's side for the most part, it's amazing how much trouble one can rile up when the staff are lavished with food and gifts during a credible sounding presentation and then asked to discuss the usage of a drug on their patients.	It's a victory for me just to learn from the staff about which drugs are preferred, and why. That info provides powerful ammunition to debate the docs with on the rare occasions that I might see them. However, it's a greater success when the staff discusses my meds with the doc after I leave. Because while a message delivered by a rep gets discounted, a detail delivered by a co-worker slips undetected and unfiltered under the guise of a conversation. And the response is usually better then what I might accomplish.	One's marketing success in a particular office can be strongly correlated to one's success in providing good food for the staff. Goodwill from the staff provides me with critical information, access, and an advocate for me and my drug when I'm not there.
Thought leaders	As a rep, I was always in pursuit of friendly "thought leaders" to groom for the speaking circuit. Once selected, a physician would give lectures around the district. I would carefully watch for tell-tale signs of their allegiance. This includes how they handled questions that criticized our product, how their prescribing habits fluctuated, or simply how eager they were to give their next lecture.	The main target of these gatherings is the speaker, whose appreciation may be reflected in increased prescribing of a company's products. Local speaking gigs are also auditions. Speakers with charisma, credentials, and an aura of integrity were elevated to the national circuit and, occasionally, given satellite telecast programs that offered CMEs.	Subtle and tactful spokespersons were the ideal candidates. I politely dismissed doctors who would play cheerleader for any drug…at the right price, of course.

These descriptions are based on SA's experience working for Eli Lilly and testimony in IMS Heath Inc. v. Ayotte, US District Court, New Hampshire. Actual tactics may vary.

doi:10.1371/journal.pmed.0040150.t001

Drug reps: How to adapt your personal style and your sales techniques according to the physician's personality

Fugh-Berman A, Ahari S (2007) Following the Script: How Drug Reps Make Friends and Influence Doctors. PLoS Med 4(4): e150 April 24 2007.

Key Opinion Leaders: How to Construct Medical Discourse to Promote Sales

Key Opinions Leaders (KOL) are influential physicians paid by the industry (~$3000/presentation) to lead educational meetings about new drugs
(around 2/3 of meetings are led by KOL, 1/3 by drug reps)

Kimberly Elliott, ex-manager of drug reps (quoted in Moynihan 2008, 1402) :

"KOL were salespeople for us, and we would routinely measure the return on our investment, by tracking prescriptions before and after their presentations. If that speaker didn't make the impact the company was looking for, then you wouldn't invite them back"

How can we measure the return on investment?
IMS Health provides the prescribing profile for each physician and its evolution over time.

The Situation Now:

1. The dominant business-model is based on me-too drugs. The financial incentives at work do not encourage innovation but, instead, lavish promotion (Demand-side without budgetary constraint).
2. Twice as much is spent on promotion as on R&D.
3. While therapeutic innovation decreased in recent years, the growth in profits has been assured by industry's increasing control over medical knowledge through the use of promotion.

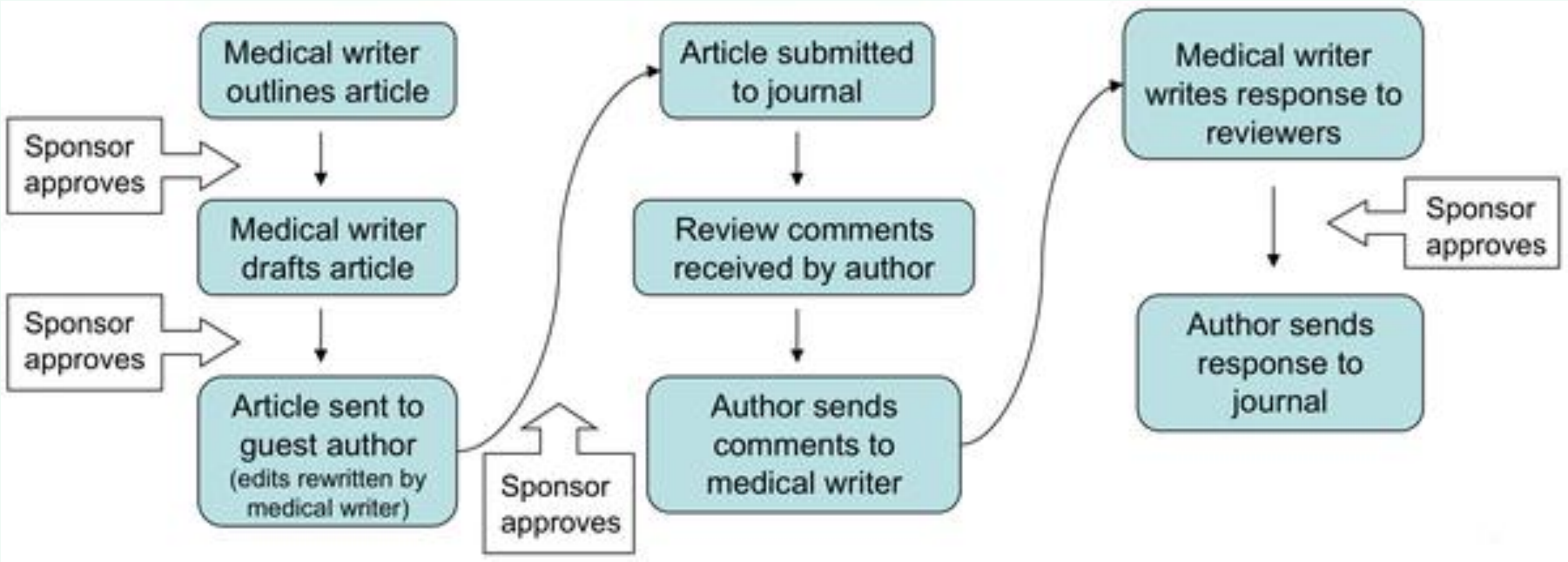
Part 3:
The Ghostmanagement of Medical Research

Ghostwriting:

Having doctors sign studies produced by agencies for publication in medical journals

- Trials are produced by Contract Research Organizations (CRO), and studies are written by medical writing agencies (MWA) whose specialty is public relations. They have expertise in taking the data and “spinning” the results to make them look more positive for the drug companies.
- CRO and MWA develop their market share not by producing good science, but by producing good marketing arguments.
- Most of the time, doctors signing their names on ghostwritten studies are not paid and they make sure that all results are solid.
- Ghostwriting of “good” studies still create medical bias because it is so widespread.

Ghostwriting Process



Are the doctors who sign ghostwritten studies corrupt?

- Doctors are sometimes paid up to $3000 to attach their names to these articles.
- Most of the time, doctors are not paid and they make sure that all results are solid.
- They might gain in reputation (sales reps showing their studies everywhere), in academic rewards and research funding.
- Ghostwriting of “good” studies still create medical bias because it is so widespread.

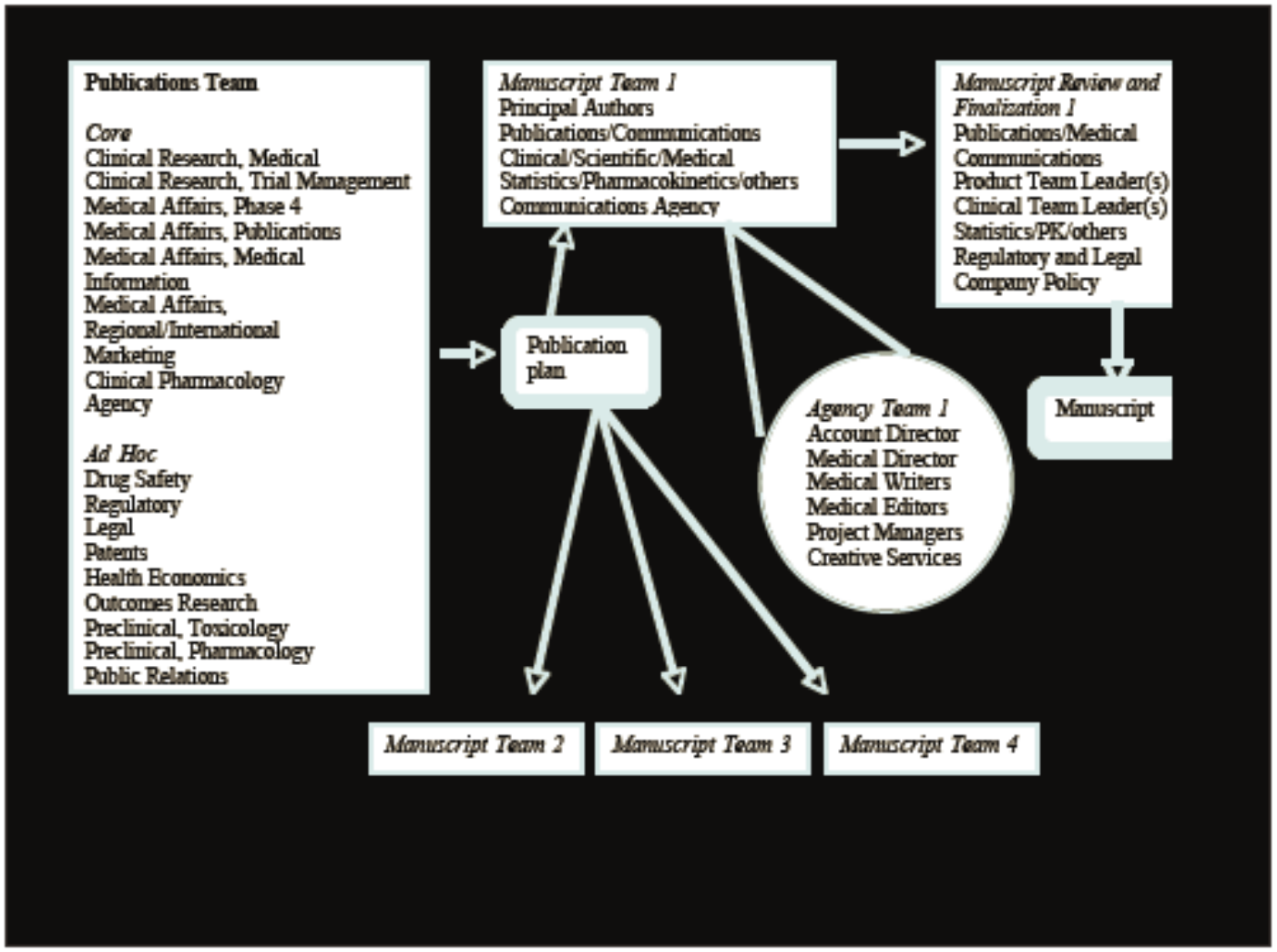
Ghostmanagement:

Organizing Medical Research as a promotional campaign

Multiplication of positive studies:

•For **Zoloft**: 85 papers produced by Pfizer out of a total of 211 papers published in medical journals about "sertraline" (40%) (Sismondo 2007).
•For **Premarin (**hormone replacement therapy):Wyeth produced at least 50 peer-review publications. (Fugh-Berman 2010)
•For **Paxil**, GlaxoSmithKline organized a ghostwriting campaign called: Case-Study Publications for Peer-Review (**CASPPER** – the friendly ghostwriting program).
•For **Vioxx**, 96 papers produced by Merck's MWA were published (Key ones omitted mentioning the death of some patients during clinical trials). Merck also produced fake peer-review medical journals like *Australasian Journal of Joint and Bone Medicine*.

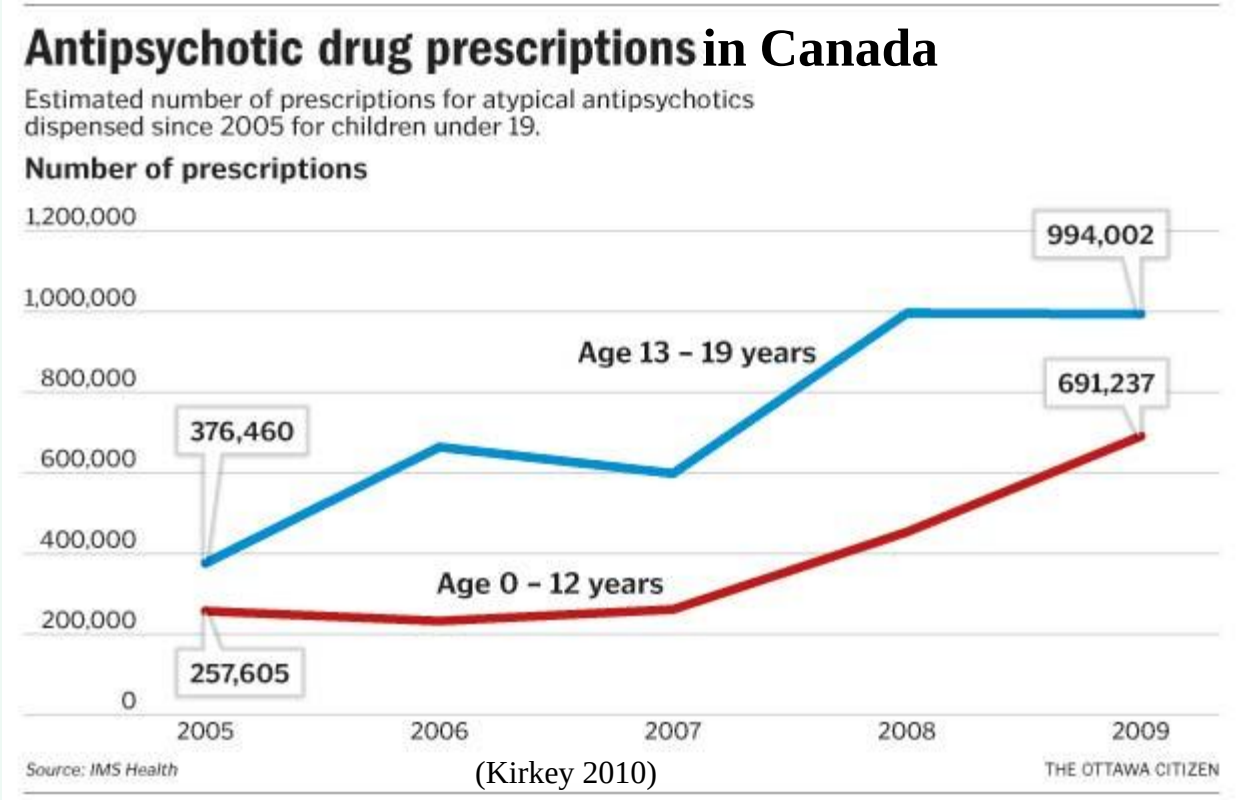
Corporate Science in Action



This slide was prepared by Sergio Sismondo after attending an international conference organized by publication planners

Ghostwriting and off-label promotion to develop market niches

-Jan 2009, Eli Lilly settled for $1.4 bn on charges of off-label promotion for Zyprexa.
-September 2009: Pfizer settled for $301 M on charges of off-label promotion for Geodon.
-April 2010, Astra-Zeneca settled for $520 M on charges of ghostwriting and off-label promotion for Seroquel.
-April 2012: J&J settled for $1.1 bn on charges of off-label marketing and non-disclosure of ADRs for Risperdal.
-One market niche to be developed was ADHD and Bipolar disorder in children.



(Kirkey 2010)

"**Perilous disconnect between the evidence base and clinical practice**"
-Helen Egger (2010)

Ghostmanagement:

Non-disclosure of negative studies:

SSRI Antidepressants: 74 clinical trials for the new generation (38 had positive results, 36 negative); 36 positive ones were published and 8 negative (including 5 as if the results were positive). (Turner 2008)

Meta-Analysis of all data submitted to FDA (most not published), showed that SSRIs were no better than placebos, except for a small difference in the case of major depression. But no adverse effects with placebos (Kirsch et al. 2008; Fournier et al. 2010)

Reboxetine for major depression: Data about 74% of patients in clinical trials were not published. When taken into account, drug no better than placebo. (Eyding et al. 2010)

Capitalizing Medical Bias

Producing the "right" medical discourse has become more profitable than producing effective drugs.

-Companies do not have a choice: those refusing to "play the game" in the name of ethics would lose market share.
-Earning-capacity is not based on producing products, but on producing medical discourses and habits of thought.
-Pharmaceutical products are not brought to the market because they have a value according to needs or social demand. Big Pharma does not produce medicines, it produces the social determinants of value.

Bias in Medical Research

What about those who produce unfavourable results?

-Vioxx: Merck drew up a hit list of "rogue" researchers that needed to be "discredited" or "neutralized":

"Seek them out and destroy them where they live" reads one internal e-mail.

8 Stanford researchers said they received threats from Merck after publishing unfavourable results.

-UofT: Nancy Olivieri (Apotex), David Healy (Prozac) (Schaffer 2004).

- Avandia (diabetes): When confronted with negative results in clinical trials, "GSK executives intimidated independent physicians [and] focused on strategies to minimize findings that Avandia may increase cardiovascular risk."(U.S. Senate Committee of Finance, 2010)

Merck's list of Rogue Researchers

NAME (Highlighted = National)	RBG	POINT RESPONSIBILITY	CONTACT INFO	AFFILIATIONS
Lawson, Jeffrey	SE (N)	1. John 2. L. Orlando	317 St. Francis Drive, #270 Greenville, SC 29601 864-235-8396	Head of Rheumatology St. Francis Hospital
Lindsey, Stephen **NEUTRALIZED**	SC	1. B. Smith 2. N. Cadena	9001 Summa Avenue Baton Rouge, LA 70809 Phone: 504-761-5481 Fax: 504-761-5702	Key for Ocshner decisions in Louisiana; chief physician for Baton Rouge, LA Arthritis Foundation
MacMillan, James **DISCREDIT**	MA	1. T. McCready	3335 Market St Camp Hill, PA 17011 717-763-0533	PCP
Mandell, Brian **NEUTRALIZED**	MA	1. T. Williams 2. G. Foster 3. D. Hartenbaum	9500 Euclid Avenue Cleveland, OH 44195 216-445-6580	Cleveland Clinic; MC affiliation: Aetna US Healthcare, Cigna, Anthem, Qual Choice
Martin, Richard W.	NC	1. M. Stelma 2. J. Harris	230 Michigan St. NE Suite 102 Grand Rapids, MI 49503 616 459 8088 fax 616 459 8312	Associate Professor of Medicine at Michigan State University
Moskowitz, Roland	MA	1. G. Foster 2. T. Williams 3. P. Davis	11100 Euclid Ave. Cleveland, OH 44106 216-844-8500	University Hospital; MC affiliation: Qual Choice

Merck's list of Rogue Researchers

NAME (Highlighted = National)	BACKGROUND PROVIDED BY A&A SPECIALISTS (with additional comments from National HSAs, RMDs, LBG, etc.)
Lawson, Jeffrey	Most influential rheumatologist in the state of South Carolina. He is in Searle Camp and speaks for them. Fall out with Merck about two months ago in regards to another doctor in his office that was being supported by Merck. Gillian Cannon and Jo Jerman are currently involved.
Lindsey, Stephen **NEUTRALIZED**	Not anti-Merck; however, he most closely fits the desired description; his facility has had a Celebrex study; has not been confirmed for a study for VIOXX to my knowledge; high influence within Ochsner System (P&T committee); submitted his name for the ADVANTAGE trial, but there were some regulatory issues that have not been worked out at this time; not sure why they have not been contacted for study participation; wants to attend advisory meetings and participate in research; has been visited by a RMD; serves on MC Advisory Board; somewhat argumentative at the Board Meeting but has been treated well by Merck; Bruce Freundlich knows him well; excellent speaker and in our camp; held off acceptance of Celebrex on formulary at Oschner pending approval of VIOXX; feels that they need to have a C-2SI on formulary and wants to review data for VIOXX; cost is an issue
MacMillan, James **DISCREDIT**	National impact; speaking extensively for Searle/Pfizer (200 days this year); numerous reports of biased and inaccurate presentations; sees few patients; Regional HSA asked him to tone down his biased presentations; gathering information on VIOXX from the Internet; one of Searle's most frequently used speakers across the nation (and loyally devoted); often claims to be more than he actually is (Rheumatologist, affiliation with Hershey Medical Center, etc.); loose cannon; written transcript of a talk was like an advertisement for Arthrotec; no way to win him over and frankly would not want this type of person speaking for my product; visit from Leo and Bruce (field report on 7/20/99) - attended consultants' meeting last year, investigator for VIOXX and MK-0663, wants us to help him be balanced
Mandell, Brian **NEUTRALIZED**	Geographical impact: physicians at Meredia Hospitals and Cleveland Clinic Program; scheduled for Grand Rounds in Toledo; not anti-Merck (actually Merck-friendly), but will only present data for approved products or information from peer-reviewed literature; will speak for Merck and was very receptive at the National Consultants' Meeting; met with Bruce Freundlich; trying to get him a gout study; neutral publication on C-2SIs because wants to see published data
Martin, Richard W.	Senior partner in Arthritis Education and Treatment Center; practice is currently recruiting another Rheum; sees patients in private practice part-time and devotes the rest of his time to research and teaching; practice has a DXA and does osteoporosis screening; upset with the way we marketed FOSAMAX and with the NORA study; brother-in-law is the Pfizer rep; Grand Rapids market, while the second largest city in the state, is very underserved with specialists (only two Rheum practices and four Rheums practicing in the area); practice located in a Spectrum Health Building (Spectrum Health created by recent merger of Blodgett and Butterworth Hospitals and Priority Health HMO) is very influential and will have a strong effect on local PCP prescribing habits; visited by Greg Bell; submitted data on his practice requesting to be considered for studies and has yet to hear from Merck on his request; did not submit his name for the ADVANTAGE trial as he would like to be considered for Phase II trials and would be offended if offered a seed study; only wants to be considered for studies if he is guaranteed authorship and if Phase II or III
Moskowitz, Roland	Geographical impact: physicians at Bedford Hospital, Geauga Hospital, Brown Memorial Hospital Geneva, Providence in Sandusky, symposium scheduled April 21, 1999, at Lake West Hospital; more balanced in presentations recently; Searle Advisory Board; good speaker and would consider using him to speak; have tried to involve in national programs, but he turned down even CME curriculum development because of his involvement with Searle

Merck's list of Rogue Researchers

NAME (Highlighted = National)	RECOMMENDATIONS (in addition to continued focus by the Specialists and HSAs)
Lawson, Jeffrey	Continued Visits From: - SBD / RBG VP - Greg Bell to call and clarify and answer clinical questions - Get a senior-level clinical visit - Currently doing research for us - Best we can do now is neutralize
Lindsey, Stephen **NEUTRALIZED**	Research (ADVANTAGE, VIGOR, etc.); invitation to Merck thought-leader event; personal visit from MRL or Marketing - Currently on Advantage - Needs to be on a larger clinical trial with VIOXX or 663 - Consultants Meeting - Visit from MRL or CDP senior-level (Dr. Geba / Dr. Bell) - RMD is presently on this team
MacMillan, James **DISCREDIT**	Strong recommendation to discredit him
Mandell, Brian **NEUTRALIZED**	Needs data; does not belong on the list. He will be a good advocate once we have some published data for him to review. There is nothing else that he needs.
Martin, Richard W.	Looking for CDP or MRL Study - Visit from a high level senior team not necessary - Greg Bell + VP Level + SBD
Moskowitz, Roland	Speaker - He is being developed by G. Foster / T. Williams and has talked for us at this time - Schedule (3 to 4) Grand Rounds in July (PA) - Could be open to do research in the future - Invite to Consultant Meetings

Impacts on Prescribing Habits: Normalized biased knowledge

<u>The case of antihypertensive drugs</u>:

-The ALLHAT study (2002) showed that the new generation of antihypertensive drugs (Angiotensin-Converting Enzyme Inhibitors and Calcium Channel Blockers), which were systematically prescribed by doctors, were in fact less effective with more adverse drug reactions than the older generation (diuretics), which costs ten times less.

-Did prescribing habits change since the study? Not at all. Companies enlisted KOL to systematically attack the ALLHAT study and offer new positive interpretations of the results (Pollack 2008).

Same results were found for antipsychotics (Jones et al. 2006).

Antidepressants next? (Healy 2008; Jureidini 2009; Spielmans 2009; Kirsch 2009).

SSRI do not work better than placebo for 70% of patients taking it. But no adverse effects with placebos (Fournier et al. JAMA 2010)

“In the ghost management of medical research by pharmaceutical companies, we have a novel model of science. This is corporate science, done by many hidden workers, performed for marketing purposes, and drawing its authority from traditional academic science. The high commercial stakes mean that all of the parties connected with this new science can find reasons or be induced to participate, support, and steadily normalize it.”

-Sergio Sismondo

Ghosts in the Machine: Publication Planning in the Medical Sciences

Social Studies of Science, April 2009; 39: 171 - 198.

Possible solutions?

- More transparency of clinical data
- Elimination and Management of COI
- More rigorous HTA
- A Possible role for Public Research?

Should we spend more on public research?

- Once taken into account all tax credits for R&D, 84% of basic research in health comes from public funding, only 12% comes from private companies. (Light 2006).
- All countries have a series of industrial policies (over patent policy):
  - Tax credits (France)
  - Direct subsidies
  - Artificial inflation of prices for patented drugs
    - Canada : + 12% as compared to France ($1.5 bn)
    - United States : prices are twice as much as in France. Medicare part D forbids to use purchasing power of the program to reduce drug costs. If the prices were the same than for Veterans, Medicare would save $12 bn.
- Funding public research does not mean to increase taxes, it is a means to reform current industrial policies, which are costly and inefficient.

Independent biomedical research is necessary:

- If we want medical knowledge to be developed as critical thinking, which purpose is to improve public health (instead of being shaped selectively, as a selling argument)
- Firms are not doing R&D to determine which is the best available treatment for a given patient, for a given condition. It does R&D to increase the sales of their products.
- Only Independent research can determine which is the best available treatment.

Example 1 - Allhat

Antihypertensive and Lipid Lowering treatment to prevent heart attack trial

- What should be the reference treatment against hypertension to prevent myocardial infarction?
- Funded by the National Institute of Health in the US to compare different types of antihypertensive drugs: Alpha blockers, calcium channel blocker, ACE inhibitors and diuretics.
- 42,000 patients followed over 5 to 8 years.
- No difference found over the main criteria (prevention of myocardial infarction), except for Alpha blockers which were withdrawn during the trial because they were clearly less effective.
- Important differences about secondary criteria: Diuretics more efficacious than ACE inhibitors in preventing cerebral vascular accidents, cardiovascular complications and heart failure, and more effective than calcium channel blockers to prevent heart failure.
- Diuretics not under patent, cost 10x less. Unfortunately, massive promotion of more recent treatments have defused the impact of the study.

Example 2 – WHI

Women Health Initiative

- At the end of the 1990s, between 30-40% of menopaused women were taking HRT.
- Purpose of the study was to find out about the long term impact of hormone replacement therapy for healthy menopaused women.
- Funded by the National Institute of Health, long-term study.
- 16,608 women, 63 years old on average, followed for 5 years.
- The trial was stopped in 2002 when it was clear that HRT had important ADRs in terms of heart disease, stroke, blood clots, urinary incontinence and increased the risks of breast cancer (8 women a year for 10,000 menopaused women receiving the HRT).
- Massive ghostwriting has been done to push HRT. The study reduced the amount of prescriptions by more than a half.

Example 3: Catie

Clinical Antipsychotic Trials of Intervention effectiveness

- What should be the reference treatment for schizophrenia, comparing efficaciousness and long term tolerance.
- Compared 4 atypical antipsychotics (Zyprexa, Seroquel, Risperdal, Geodon) and perphenazine (unpatented typical antipsychotic).
- Atypical antipsychotics were shown not to be more efficacious or have less important ADRs than typical antipsychotics.
- Monthly cost for atypical antipsychotic: $600.
- Monthly cost for typical antipsychotic: $ 50.

Example 4: Agenzia Italiana del Farmaco

-Italian equivalent of Health Canada.

-Interesting experience from 2005-2008: 5% tax on all pharmaceutical promotional expenditures. Money would be used to fund independent clinical trials.

-AIFA collected 40 M Euros/year and funded studies and trials for orphan drugs, for patients normally excluded from clinical trials, trials to determine reference treatments, and studies to promote the rational use of medicines.

Producing economic value in the pharmaceutical sector?

-Not by innovating and producing wealth! (traditional understanding of accumulation of value in capitalism)

-By directly producing the social determinants of value through massive scientific bias and lavish promotional campaigns.

-The shaping of knowledge and science has become the central focus of the creation of value.

-Science is becoming the battlefield for corporate interests.

-As long as the Academia grovels for more partnerships with corporate interests, it loses its autonomy and becomes part of this battlefield corrupting scientific research.

Conclusion:
The Emergence of Corporate Science

-Not confined to medical research and faculties of medicine (Tobacco; climate-science; GMOs; Energy; Everything that relates to Risk Management in for-profit sector).

-Pharmaceutical Sector has perfected the art of corporate science, and has shown how profitable it can be.

-Science is becoming a battlefield, and the promotion of university-industry collaboration transforms the purpose of universities, and transforms academics into soldiers.

-But the Academia comes from a strong tradition, with a strong ethics about how (and why) scientific research must be done. There is still possibility for strong resistance.

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Translated from *Rev Prescrire* April 2012; 32 (342): 311-314

Corporate influence over clinical research: considering the alternatives

This text is based on a presentation delivered during the annual Prescrire Awards ceremony in January 2012 by Marc-André Gagnon, PhD, Assistant Professor in Public Policy at Carleton University (Canada) and Research Fellow in Ethics at Harvard University (USA). Videos of the presentation (in French) are available online at english.prescrire.org, search with the terms "video" and "gagnon".

Abstract

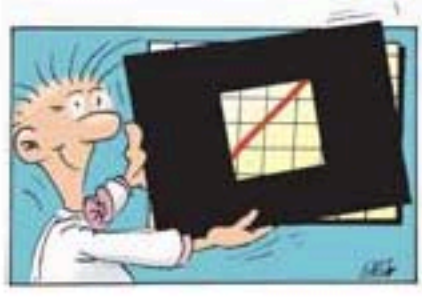
● The dominant business model of the pharmaceutical sector is based on the massive promotion of drugs that often do not represent any significant therapeutic advance.

● Clinical research is therefore run like a promotional campaign. The data obtained from clinical research are primarily used to boost and support sales rather than to improve prescribing behaviour.

● Three common and widely used corporate strategies are used to this end: ghostwriters are employed to inflate the number of publications showing the drug in a positive light; results that would harm sales are not published (publication bias); and negative data are suppressed, sometimes going as far as to intimidate troublesome independent academics and whistle-blowers. The objective of these strategies is to enable the new drug to gain market share from its competitors.

● If medicine is to progress, research must be more independent and freed from the commercial imperatives of the pharmaceutical industry.

Rev Prescrire 2012; 32 (342): 311-314.



Can we trust the results of clinical research as it is currently conducted? Since clinical research is mainly run by pharmaceutical companies, we cannot answer this question unless we understand the business model and the financial incentives behind the clinical research these companies conduct. We will therefore briefly analyse the predominant business model, which is based on massive promotion of drugs that too rarely represent any significant therapeutic advance, then we will analyse the nature of private-sector clinical research and explore the opportunity to develop a more independent approach to clinical research.

Profits without innovation

Between them, the 15 biggest drug companies share two-thirds of the global pharmaceutical market, worth 900 billion dollars. These companies spend about twice as much on promotion as on research (1). Their business model is based on the massive promotion of new drugs that often only extend an existing product line and offer no advantage over existing treatments.

A longstanding crisis in innovation. The vast majority of the new drugs introduced onto the market since 2010 provide no significant advantage over existing treatments. For over 30 years, *Prescrire* has been systematically analysing whether or not each new drug introduced onto the French market represents a therapeutic advance. By pooling all of the data collected since 1981, we can see that the proportion of drugs that represent no significant advance has been increasing, particularly in the last 10 years, as has the proportion of drugs with a negative harm-benefit balance (see figure 1) (a)(2).

For example, in 2009, *Prescrire* analysed 109 new drugs or indications (excluding generics): 3 were considered a minor therapeutic breakthrough, 76 added nothing new to the existing pharmacopoeia, while 19 were deemed to represent a possible public health risk (2). In Canada, the Patented Medicine Prices Review Board has been classifying newly patented drugs in a similar way since 2010. The results are comparable: nearly four-fifths of new patented drugs provide no therapeutic advantage over existing drugs on the Canadian market (3).

With innovation at a virtual standstill for decades, the pharmaceutical industry became conscious that it needed to change its model. However, the business model based on the massive promotion of drugs that are not truly innovative continues to thrive. It is quite simply the most profitable financial model. For example, the chairman of Sanofi-Aventis, Jean-François Dehecq, may well maintain that the "Pfizer model", in which twice as much is spent on promotion than on research, is now dead (4), but Sanofi-Aventis's financial reports show that in 2011 it still employed twice as many sales personnel as research staff. ▶▶

Profits continue to grow. While standard economics might dictate that the market would penalise the lack of innovation in the pharmaceutical sector, drug company profits are actually soaring. It is difficult to conduct a historical analysis of the profitability of the global pharmaceutical industry because aggregated data are not available. However, 8 of the 15 major drug companies are American. Focusing on the dominant US pharmaceutical companies (from *Fortune* magazine's ranking of the 500 largest companies in the US) and comparing them with the other Fortune 500 companies, their rising average returns show that the sector is highly profitable (see figure 2) (b)(5).

The massive promotion of new drugs has a decisive role in ensuring that they are widely prescribed, even if they are no more effective than older drugs (5). Antipsychotics are a prime example of this. A "new generation" of antipsychotics was systematically prescribed by doctors, yet these drugs proved to be no more effective than the prior generation and were 10 times more expensive (6).

The current business model, based on aggressive promotion and meagre innovation, remains a huge financial success. Why would drug companies abandon it?

Institutional corruption of clinical research

In the current business model, pharmaceutical companies devote most of their resources to influencing medical practices rather than to developing and producing drugs. This involves generating medical knowledge tailored to support sales growth (5). Clinical research is therefore run like a promotional campaign, aimed at generating selling points to help market the product, rather than at putting out reliable scientific data (5,7).

To ensure that the scientific knowledge generated is profitable for the company, three corporate strategies are used to "ghost manage" research: the number of publications of studies that show the drug in a positive light is inflated; information that could harm sales is suppressed; independent academics are intimidated (or even "neutralised").

Inflating the number of favourable publications. Studies written for drug companies by ghostwriters do not come about as exceptions: they form part of carefully thought out publication plans that are essential to the success of promotional campaigns and the market launch of a new drug (8).

Here are some examples. Internal documents from Pfizer revealed that, between 1998 and 2000, the company directly initiated the writing of no fewer than 85 scientific articles on the antidepressant *sertraline* (Zoloft®). During this period, the entire scientific literature on this active substance consisted of only 211 articles (9). In this way, Pfizer produced a raft of articles showing the drug in a positive light, lessening the impact of the critical studies. Wyeth generated about 50 articles in favour of hormone replacement therapy (10). Merck mounted a ghostwriting campaign to promote its now-infamous drug *rofecoxib* (Vioxx®): 96 articles were published, some of which omitted to mention the deaths of patients who participated in clinical trials of the drug (11). GlaxoSmithKline ran a secret campaign to skew the literature in favour of its antidepressant drug *paroxetine* (Deroxat®, Seroxat®, Paxil®). They called it "Case Study Publication for Peer-Review", or CASPPER for short, in reference to the well-known "friendly ghost"... (12).

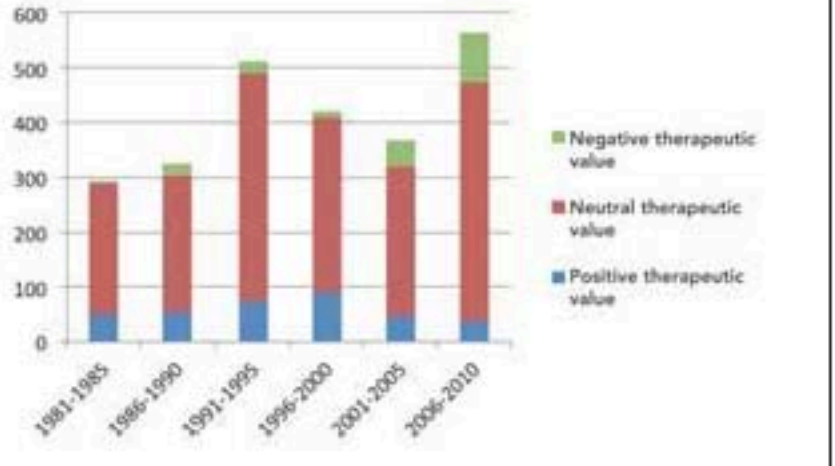
Suppressing the publication of results that could harm sales. Pharmaceutical companies consider that private-sector clinical research produces private, confidential results that are their own intellectual property. They assume the right not to publish certain results, in the name of trade secrecy. And they are not compelled by political and health authorities to make public the data obtained in clinical trials. Drug companies can therefore select which data they want to see published.

For example, major pharmaceutical companies have systematically failed to publish unfavourable studies on a "new generation" of antidepressants, the so-called selective serotonin reuptake inhibitors (SSRIs). Of the 74 clinical trials that were conducted on these antidepressants, 38 produced positive results, while the other 36 showed the drugs to have questionable or no efficacy. However, while 94% of the positive studies were published, only 8% of the unfavourable studies were published as negative results, and 15% of the negative studies were published in terms that suggested that the results were positive! (13). Doctors reading the scientific literature got a biased view of the "benefits" of SSRIs, which explains why they so readily systematically prescribed these antidepressants to their patients. The scientific data show that for 70% of the patients taking SSRI antidepressants, the drugs are no more effective than a placebo (14), but unlike a placebo SSRIs are associated with serious adverse effects (e.g. an increased risk of suicide).

Intimidating and even neutralising troublesome independent academics and whistle-blowers. A third strategy, which is more widespread that one might think, is to intimidate and neutralise independent researchers who produce studies that show the product in an unfavourable light. The case of Irène Frachon and *benfluorex* (Mediator®) is well known in France (15). But it is not exceptional. Merck's internal e-mails, which came out during lawsuits over the harm caused by its drug *rofecoxib*

Figure 1

***Prescrire*'s ratings of new drugs and new indications since 1981**



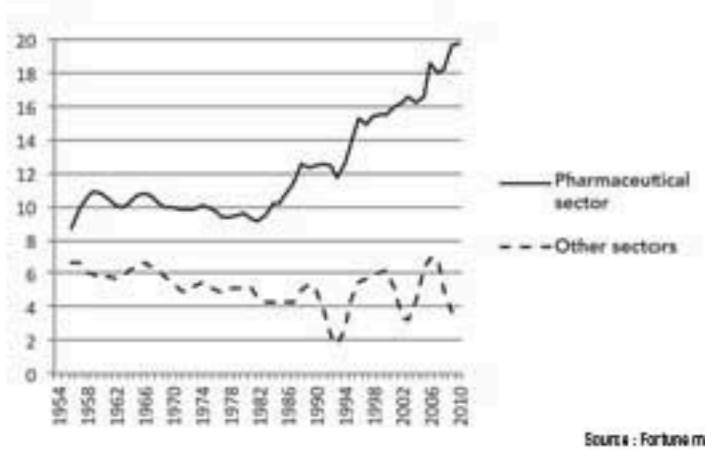
Source : *Prescrire* (a)

a- The categories used here are a simplified version of those used by Prescrire. "Positive therapeutic value" corresponds to a Prescrire rating of "Bravo", "A real advance" or "Offers an advantage". "Neutral therapeutic value" includes Prescrire ratings of "Possibly helpful" and "Nothing new". "Negative therapeutic value" equates to the Prescrire rating "Not acceptable".

(Vioxx®), revealed that the company had drawn up a hit list of "rogue" researchers who had criticised Vioxx®. One e-mail recommended that the researchers on the hit list had to be *"discredited"* and *"neutralized"*. *"We may need to seek them out and destroy them where they live"* read one of the e-mails. This intimidation was the result of the work of an entire team that systematically monitored everything that was said about the product (16). Similarly, in the case of the antidiabetic drug *rosiglitazone* (Avandia®), which was withdrawn from the market in 2010 for safety reasons, a report by the US Senate explained that the main strategy of GlaxoSmithKline executives when confronted with the publication of negative clinical results was to downplay the importance of these results and to intimidate independent researchers (17).

Figure 2

Average net profit margin of the dominant US pharmaceutical companies and other dominant US companies: 1970–2010 (average over 3 years)



Source : Fortune magazine

In short. These three corporate strategies are ubiquitous. They corrupt medical research. It is an institutional, indirect form of corruption, acting through an economy of influence that pervades the whole of research and ultimately skews the scientific knowledge on which medical practice is based.

The vast majority of researchers are honest people who seek only to make a positive contribution to medicine, but because of the economic structures and the web of influence within which they operate, they often become unwitting pawns in a system in which shareholder profits are maximised at the expense of patient safety.

It would be inappropriate to blame drug companies for this state of affairs, because they have no choice. A company that refused to play the game for ethical reasons would rapidly lose its market share. In the current business model, pharmaceutical profits depend on the company's capacity to shape medical knowledge and create market niches, rather than to develop innovative treatments that improve patient health.

How can truly independent research be achieved?

Several fundamental reforms are needed in order to improve research practices. Transparency in clinical research is crucial: all of the results of clinical trials, whether financed by public or private funds, should be made publicly accessible. The regulation and elimination of conflicts of interest in medical research is also a main concern. Improvements could also be achieved by conducting a more rigorous clinical and pharmacoeconomic assessment of new drugs and linking profit margins to therapeutic value. However, the most urgent reform is to re-establish a high opinion for independent research.

The case for freeing research from drug company control. In the current situation, where short-term financial incentives shape research, a reliable way of ensuring profitability is to simply repatent an existing drug. One need only alter the structure of the active substance slightly and mobilise an army of sales reps when the drug is launched to influence doctors' prescribing behaviour in favour of the "me-too" drug (c).

The pharmaceutical industry currently occupies a central role in all medical research, and public-sector research has merely a supporting role. There are some who feel that public-sector research is inferior, as if it were worthless without the involvement of the pharmaceutical industry.

Yet, clinical trials can only be free from any commercial considerations when conducted in an independent, not-for-profit research setting. And in fact, public-sector research already makes a huge contribution to drug discovery (18). A study published in 2011 revealed that, between 1998 and 2005, public-sector research contributed to the discovery of nearly two-thirds of the drugs that represented a genuine therapeutic advance, but contributed very little to the development of the products that provided no significant benefit relative to existing drugs (19).

Can we afford more funding for public-sector research? The question needs to be reframed, because contrary to popular belief, research is already largely funded from public sources. For example, once tax credits for research and development expenditure are taken into account, public funds pay for about 84% of basic health research, while the pharmaceutical industry contributes only 12% (20).

Governments also commonly offer a range of incentives to support their own pharmaceutical industry: direct subsidies, lax pharmacoeconomic assessments, extended exclusive rights, or generous pricing and reimbursement policies. For example, France offers the most generous system of tax credits for research and development (21), while Canada chooses to artificially inflate the price of patented drugs, where they cost about 10% more than in France. This policy adds about 1.5 billion Canadian dollars to the country's medicines bill, yet after tax credits have been taken into account, the pharmaceutical companies in Canada spend a net total of only 610 million Canadian dollars on research and development (22). In the US, public authorities do not intervene to reduce the costs of patented drugs. The prices are therefore double those in France. If the government allowed only one of the public health insurance schemes, *Medicare*, to negotiate minimal discounts on patented drugs, American taxpayers could save around 12 billion US dollars a year (23). ▶▶

b- For a detailed presentation of the methodology used and a more thorough analysis of the sector's profits, see reference 5.

c- A "me-too" drug, sometimes called a line extension, is a drug derived from an existing drug that is already marketed and often widely used, by slightly modifying the chemical structure of the active substance.

Funding public-sector research should not be viewed as an additional cost, but as the means of reforming the expensive and ineffective current industrial policy.

In summary. As long as pharmaceutical companies hold the purse strings of biomedical research, medical knowledge will be selectively constructed for the purpose of marketing drugs rather than improving public health.

So long as public institutions continue to court partnerships with subsidised pharmaceutical companies, the way will remain wide open for the continued institutional corruption of scientific research.

Marc-André Gagnon

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*- In accordance with the French decree of 25 March 2007: Art. R. 4113-110 of the French public health code.

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