

The Dominant Business Model in the Pharmaceutical Sector:

Profits Based on Control over Medical Knowledge

Presentation for

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OUTLINE

Part 1: Overview of the political economy of the pharmaceutical sector.

Part 2: A global view of pharmaceutical promotion

Part 3: Impact of promotion on medical practice, education and research.

Part 1:

Overview of the political economy of the pharmaceutical sector

Some indicators

- In 2008, the global market for pharmaceuticals was around US\$750 billion, representing 3.3% of the world's industrial production. (According to IMS Health)
- From 2000 to 2008, the average annual increase in world GDP was 4.1%, while average annual pharmaceutical sales grew by 8.7%.
- In Quebec, pharmaceuticals represented 8.3% of all health spending in 1985, and 20.7% of all health spending in 2008. The growth in spending on pharmaceuticals accounts for more than 25% of the growth in total healthcare expenditures. (According to ICIS)

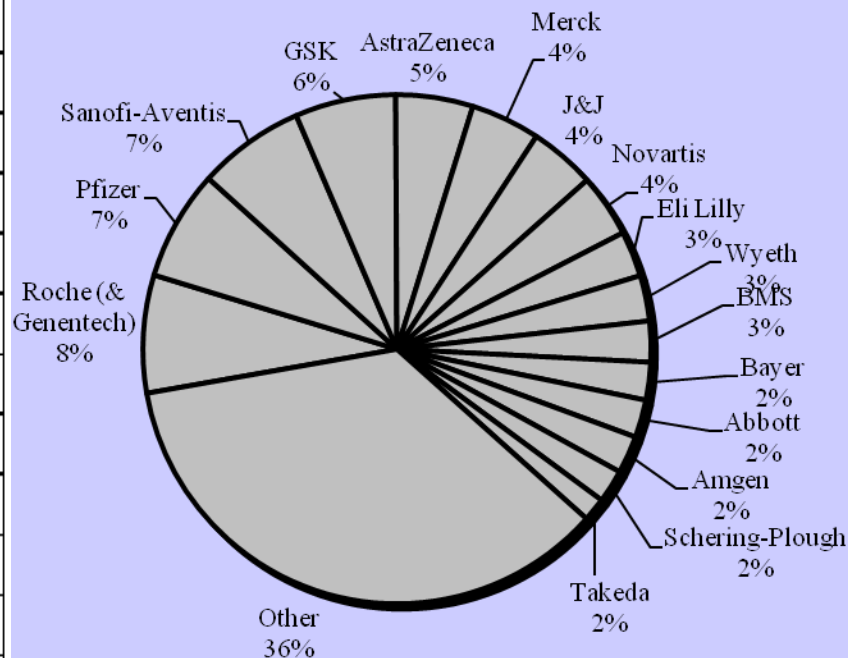
List of Big Pharma Companies, Sept. 30 2008

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

Big Pharma = 64% of world sales

Drug Sales as a Share of Total Market, 2007



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

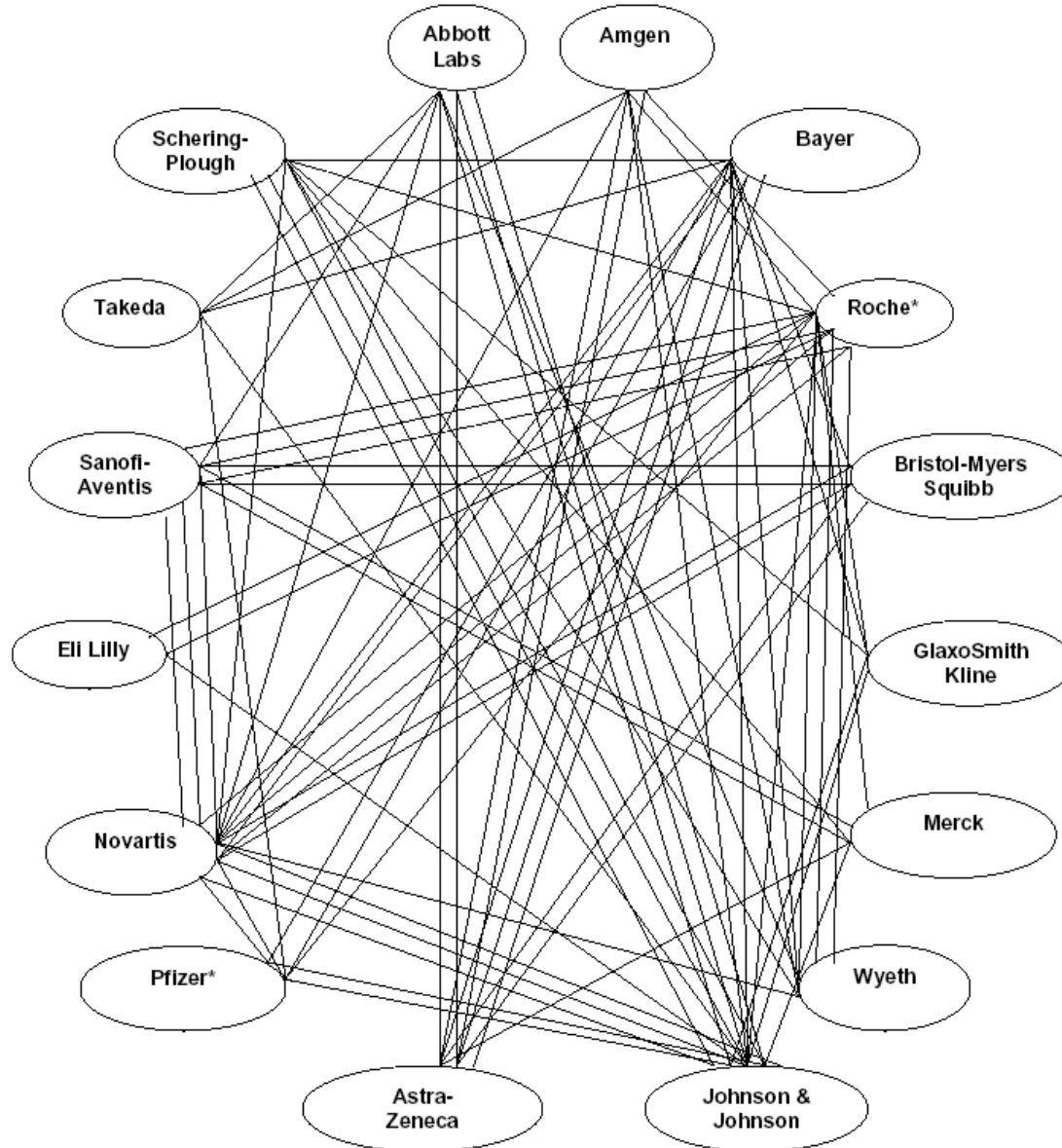
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On-Going Cooperation Agreements Among Big Pharma, May 2008

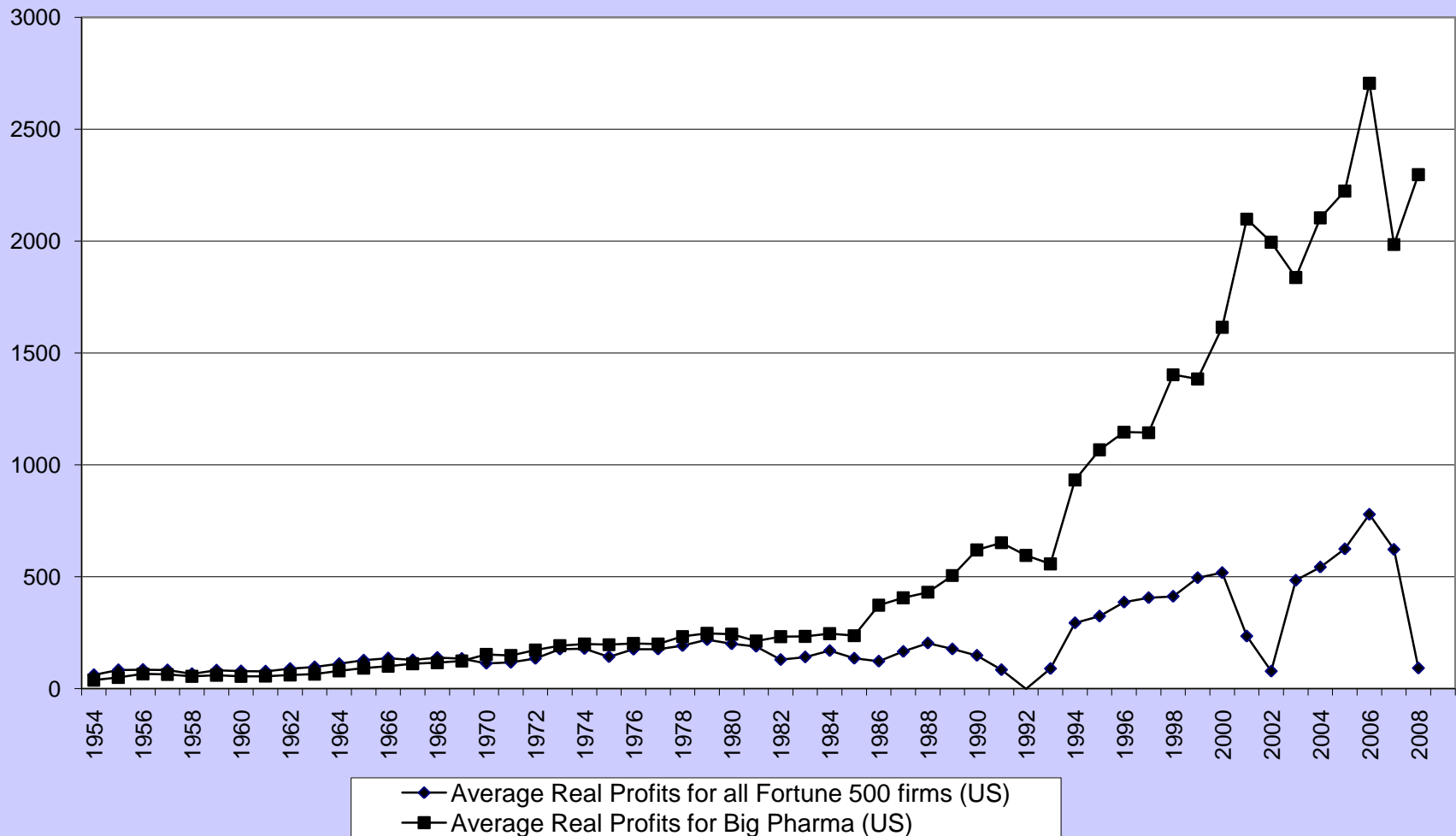
Source: Bioscan and Bioworld



Big Pharma Differential Accumulation;

Average profits of US dominant pharmaceutical firms as compared to average Fortune 500 firms (1954-2008; in millions of constant 1984 US\$)

Source: Fortune

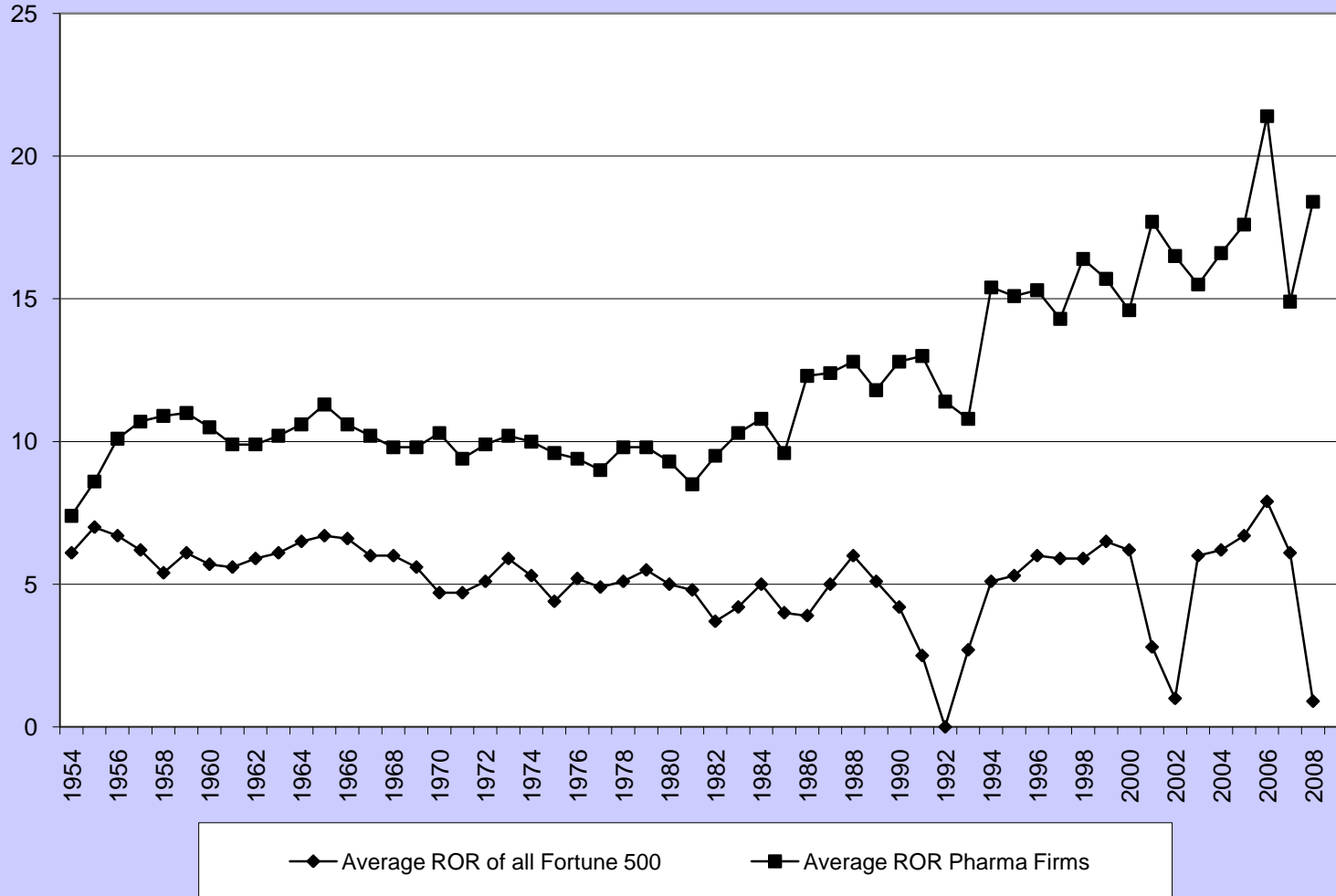


Differential Evolution in the Rate of Profit

Return on revenues (Profits per unit sold)

1954-2008

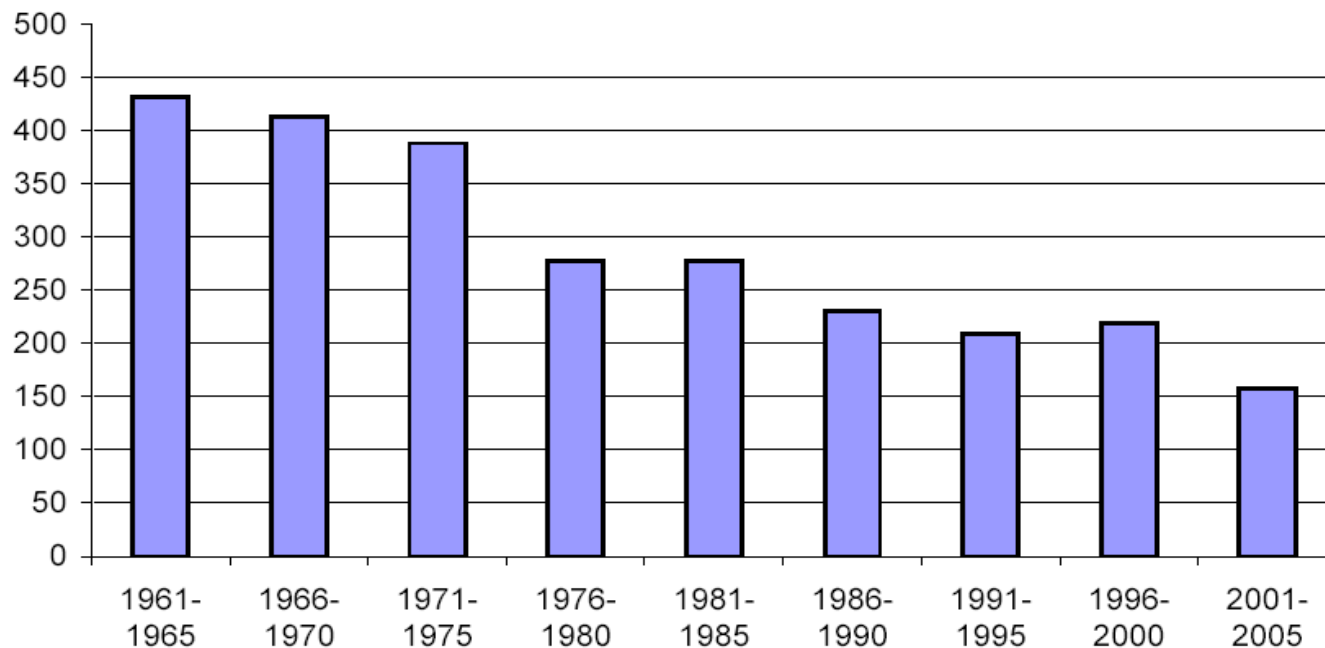
Source: Fortune Magazine (Updated May 2, 2009)



Are We Entering a New Era of Innovation?

A Quantitative Analysis

Global Introductions of New Chemical Entities 1961-2005



Sources:

1961-1985: Erika Reis-Arndt (1987) cited in Redwood (1987)

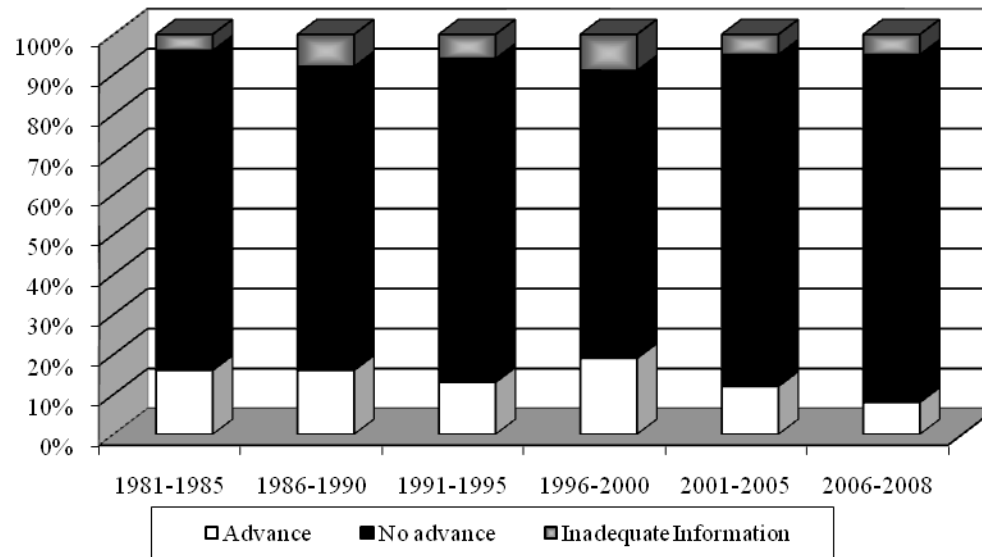
1986-2003: IMS Lifecycle New Product Focus Database cited in Grabowski and Wang (2006)

2004-2005: IMS Lifecycle New Product Focus Database cited in IMS Health Canada (2006).

Are We Entering a New Era of Innovation?

A Qualitative Analysis

Percentage of New Drugs Representing a Therapeutic Advance in the French Pharmacopoeia, 1981-2008



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

- In 2008, 120 new drugs were introduced in France.
- 6 were considered a therapeutic advance.
- 105 did not bring anything new to the existing pharmacopoeia
- 23 were harshly criticized by doctors since they represented potential danger to health

Part 2:

A global view of pharmaceutical
promotion

What is the Impact of Pharmaceutical Promotion?

- **In Theory:**

- ↑ **Promotion = ↑ Units sold**

- ↑ **Total costs of production, but**

- ↓ **Average Cost per unit, so**

- ↓ **Prices**

What is the Impact of Pharmaceutical Promotion?

In Practice: «Charge what the traffic will bear!»

– **Avastin:** Anticancer drug (bevacizumab) costs \$17-\$50 for an injection, when used off-label to treat Age-Related Macular Degeneration (ADM). But the manufacturer, Genentech, refused to seek authorization of this drug to treat ADM. Instead, it produced a derivative, Lucentis (ranibizumab), under a new patent. Lucentis costs about \$2000 per injection. Lucentis is not more efficacious than off-label Avastin at the right dosage, but Avastin is much more cost-efficient. Genentech has restricted sales of Avastin for ophthalmic use, and deploy great energy to discredit the use of Avastin for ADM, in spite of clinical evidence. (Raftery et al. 2007)

What is the Impact of Pharmaceutical Promotion?

In Practice: «Charge what the traffic will bear!»

Sarafem: When Prozac's patent expired, the manufacturer, Eli Lilly, developed a new niche for the product using an important promotional campaign about Pre-Menstrual Disphoric Disorder (You think it is PMS, It could be PMDD!!!). They turned Prozac into Sarafem: same molecule, same dosage, new color (lavender and pink instead of blue), new patent. The price was three times higher than the price of Prozac (while patent protected), and ten-times higher than generic Prozac.

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

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

Understanding the proportions:

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



Promotion still Growing...

From 1996 to 2004, in the United States:

- The number of physicians increased by 38%.
- The number of drug reps increased by 150%.
- The number of promotional meetings increased by 254%.
- The Top 10% prescribers received from 2 to 4 times more visits from drug reps.
- The private funding of continuing medical education (CME) increased by 465%. Private funding now accounts for more than public funding in CME.
- Direct-to-Consumer Advertising for pharmaceuticals increased by 509%.

What is the situation:

- 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:

Impact of promotion on medical practice, education and research

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.

Physician Category	Technique	How It Sells Drugs	Comments	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.	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 than 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.
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 around and other reps are less likely to invest resources in them.	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.
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 unrestricted "educational" grants so loosely restricted that they were the equivalent of a cash gift, although I did not personally provide any grants.	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			
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.	<h1>Drug reps: How to adapt your personal style and your sales techniques according to the physician's personality</h1> <p>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.</p>			
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.				

Big Pharma's Influence over Medical Research

- Deploy R&D funding according to putative market “niches”
- 70% of firms' external R&D funding goes to Contract Research Organizations (which should be considered public relations firms), 30% goes to universities, but with non-disclosure clauses.
- Ghost writing of a critical mass of articles in medical journals
 - Sertraline (Zoloft): 85 papers produced by Pfizer on a total of 211 papers published in medical journals with “sertraline” in title, or 479 as keywords (Sismondo 2007)
 - Fake Journal: *Australasian Journal of Joint and Bone Medicine* (by Merck for Vioxx)
- Non-disclosure of negative studies:

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

Zetia/Vytorin: Since 2006, clinical trials clearly showed that Zetia did not bring any benefit over Zocor to reduce heart attacks (patient had to take the drugs combined as Vytorin). 1 million prescriptions were made every week until 2008, which amounted to \$2 billion in sales for a product that did not bring any benefit over the much cheaper Zocor alone. (Berenson 2008)
- Cherry-Picking results and KOL: Producing the “right” medical discourse is more profitable than producing effective drugs.

Phase IV Clinical Trials (postmarketing)

- 13.2% of R&D Budget spent for Phase IV clinical trials.
- 75% of these trials are set up only for promotional purposes (seeding trials).
- The purpose is to mobilize doctors by making them believe they are participating in the progress of science.
- Studies are done on large populations; Doctors are normally paid between \$100 and \$500 per enrolled patient.
 - 34 033 Canadians enrolled for Diovanantage (Diovan, Novartis), to analyze their compliance (How can Merck's product Cozaar compete with Diovan now?)
 - 4500 Patients enrolled in Montreal/Quebec/Chicoutimi for Obstat (funded by Pfizer and Astra-Zeneca) to analyze compliance with statins for "new patients only".
- However, the lack of good Phase IV clinical trials (or non-disclosure of results) is precisely what hinders a good assessment of a drug's risks when used in a large population.

Impacts on Prescribing Habits

The case of antihypertensive drugs:

-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. Firms 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).

New Trends in Pharmaceutical Promotion

- Increasing Budget for KOL and CME.
- Patient-Support Programs for Blockbuster Drugs (i.e. CV Success Zone). [See the critical analysis by IGAS 2007; Biron et al. 2009].
- Empowering patients through Direct-to-Consumer Advertising [Canwest, Celebrex, Gardasil].
- Creating Fake Medical Journals: Merck created the *Australasian Journal of Joint and Bone Medicine* + 21 other journals published by Elsevier.
- Organizing promotional campaigns around off-label uses of drugs (i.e. Neurontin and Zyprexa). [See Steinman et al. 2006; Spielmans 2009]
- Focusing on “emerging markets” because they offer more opportunity to “educate” doctors, as they face more and more restrictive laws in OECD countries.

The Main Problem

Even the most competent doctor can no longer be assured of obtaining unbiased and objective information which would allow him to prescribe the most efficacious products for his patients. Pharmaceutical promotion, having invaded every aspect of medical practice, has led the doctor to prescribe products that offer dubious therapeutic value, but better financial returns to pharmaceutical firms.

Promotion does not serve patients or public health; it serves shareholders. And, little by little, it is killing off pharmaceutical research and medical ethics...

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