QUEST CLUB

The Pharmaceutical Industry,

Orphan Drugs,

R & D and Profits

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Thanks to librarian Sharon Hultquist who shared some book titles which helped me start my research. Thanks also go to pharmacist, Gordon Bokhart who pulled some articles for me. And, of course, thanks to my son Grant and husband John who are always eager to hear me talk more.

For full disclosure, I have not been paid by any drug company to be here today; I personally take no prescription drugs but wonder if today I should have tried both the little purple pill and perhaps some Kaopectate.

While I am pleased with my good health and you might be as well, we must remember the quote in the book *Selling Sickness*:

"If you think you are healthy, you just haven't had enough tests." (Moynihan and Cassels, 2005, p. 150)

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I've organized this paper into three parts: The Good, The Bad and The Ugly. In the "good" section, you'll hear about some wonder drugs and a bit on orphan drugs; the "bad" section will shine a light into some dark practices including marketing, while the "ugly" section will reveal some very unsettling information about drug research. I've put the good, the bad and the ugly in reverse order because I'd hate to leave you on a downer which I fear would force you to request a prescription for Cymbalta.

Naturally, it's the ugly, that I think, will hook you in. If that doesn't do it, I'm hoping the pens on your table will be incentive enough for you to stay with me on topic. I would have brought donuts as the pharmaceutical sales representatives often do, but I didn't want to be that cliché.

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For a bit of background, the entire pharmaceutical industry started in the dirt which isn't even the "ugly" part of our story; it's just where our drugs first began - as botanicals. One drug that comes to this Indiana gardener's mind is willow bark. Some of you might have it in your backyard in the form of white willow, European willow or pussy willow; the bark contains salicin which is chemically similar to aspirin; it was thought, at the time, to be helpful in decreasing aches, pains and fever. People were advised to suck on the bark. It was used in the time of Hippocrates for some of the same reasons we use aspirin today.

We could probably trace the first pharmacies back to the middle ages and without drive-throughs, we can all agree they must have been Medieval. Ground work was laid on our modern day pharmaceutical industry, most likely with the discovery of insulin around 1920 which was manufactured and distributed by Eli Lilly in 1923. The second leading driver to the drug industry of today was probably penicillin, discovered in the late 20's but not put into widespread use until the early in 1940's.

Another notable period for the pharmaceutical industry was the early 1960‘s. The boom in the drug industry was brought about in large part by The Pill and Valium. Valium had the distinction of being the top selling prescription drug for over 13 years.

But it was the anti-nausea drug, thalidomide, that brought about changes in regulations for oversight, drug use and clinical trials. Discovered in Germany in the late 50‘s it came to be widely used as an anti-emetic, sedative and tranquilizer in the early 60‘s. Its connection to birth defects was one of the driving forces for drug regulation in the US through the Food and Drug Administration, the FDA.

The last important date I’ll mention is 1981 when direct-to-consumer advertising was permitted; this seemed to dramatically change the industry forever.

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The pharmaceutical industry is the fifth largest in the US after oil/gas, retail, healthcare and automotive. Among the Fortune 500, 12 pharmaceutical manufacturers are listed including: Pfizer, Johnson & Johnson, Merck, Abbott and Lilly.

It is estimated that 70 percent of Americans take prescription drugs the most common of which are the categories of antibiotics, antidepressants and pain medication. That, of course, does not take into account the medicinal before-dinner cocktail.

THE UGLY

For the ugly portion of this paper**,** I’ll focus on the “who” and “what” of the issue mostly on the research side of the industry. The who includes scientists as well as medical journal publishers, drug companies and the foreign contractors they hire to conduct drug trials.

The medical community is always looking for the gold standard in research: randomized, controlled trials. This design format decreases the likelihood that you get a result from pure chance. It levels the research playing field, eliminates as much bias as possible, but, even these studies have inherent problems.

Study subjects are randomly assigned to be a participant in either an experimental group or a control group. The study is conducted and the only expected difference in outcome between these two groups is the variable being studied. For this discussion: was the drug effective or not?

Most of us think that new drugs are brought to the market because they are an improvement over what is currently available. But, an often used misdirection is to test the new drug against placebo and not against a drug currently being sold. If you can prove that your drug is better than nothing, you’ll most likely get a thumbs up from the FDA.

There were 197 new drugs approved between 2000 and 2010; of those, only one-third of them had published research showing how this new drug fared against a drug already on the market.

But, even if this new molecule is tested against a drug already being sold, it may, be compared using incorrect dosing of the already approved drug. Most of us could agree, that either too low or too high of a dose of the older drug, can influence outcome.

So, if I want to see if my new antibiotic erythromycin works, I can hire Chinese researchers to compare my drug against placebo or I can ask them to compare my antibiotic against, say, 1/4 dose of penicillin. It's quite likely that my correctly dosed erythromycin will show a better result than the insufficient dose of penicillin.

Drug company research can fail us in several other ugly ways.

Sometimes, the test subjects aren't representative of the patients who will ultimately use the drug. Sometimes the drop out rate from trials goes unreported. Sometimes the conclusions are not supported by the data that is published. Sometimes researchers choose not to submit negative findings to journals. But the most damaging aspect is not publishing data that IS available and accurate.

A pharmaceutical company, say Pfizer, can fund 10 studies on a drug, let's say Glucotrol, their drug to lower blood sugar. But if only one of those studies shows what Pfizer wants it to show, that may be the lone study submitted for publication. Prescribing physicians will be unaware of the other nine studies that might have shown no benefit or harmful side effects.

Ben Goldacre, physician and author of *Bad Pharma,* further suggests there are no published reports on half of the research that is begun.

And, there is also publication bias. Journals seem to prefer publishing positive over negative results. Medical journals are supported, of course, primarily by the pharmaceutical ads within their pages.

To expose and quantify this idea, there was a study about studies. In 2008, the *New England Journal of Medicine* published an article of a systematic review of anti-depressant drug trials. They looked at new antidepressant drugs approved by the FDA over a 15 year period.

Of 74 studies conducted in that time, 38 had positive results and 36 had negative results. Almost the same number. Which studies were selected for publication?

Thirty-seven of the positive studies (that's all but one) got published. Of the negative studies, just 3 were published. This is significant because physicians make decisions to treat patients based on published data. Doctors want to practice evidenced based medicine. But, if data is missing, informed decisions are difficult to make.

Drug companies began to outsource their clinical trials when the costs of managing them within the US became too expensive or troublesome. Eli Lilly was criticized for their drug trials in the US as recently as 1996; they were recruiting homeless alcoholics to be subjects in their trials so, to avoid further public criticism, Lilly opted to employ outside companies to do their testing.

The name for these companies are clinical or contract research organizations or CRO's which now are a $20 billion industry. In 2008, there were 9000 patient studies being conducted by CRO's in 115 countries. The countries with the greatest number of CRO's are India and China.

Subjects are paid for their participation in clinical trials. The *Journal of Medicine and Philosophy* in a 2002 article suggested payments should be high enough not be exploitive but not so high that being a test subject is irresistible.

Two questions that might be asked with this issue. Is it right to use subjects who might never benefit from the drug being tested? And, if these test subjects could benefit from the drug, but may not be able to afford the drug if it ever comes to market, is that ethical?

A separate concern is if that test population might metabolize that specific drug being tested differently than the target population. Many foreign test subjects suffer from malaria and tuberculosis which might change the way a person reacts to a drug.

The Bristol-Myers Squibb drug, Pravachol, prescribed to decrease the risk of stroke acts by lowering cholesterol and triglycerides. More women have strokes than do men, yet, in the pravachol research more male subjects than females were studied. We don't know if the results would have been different if the study subjects had mirrored the population who would be treated by this drug.

How do drug companies using CRO's see the process? From Gilead Sciences, a biopharmaceutical company's quarterly report to its investors in 2009 stated:

"Due to our reliance on third party contract research organizations to conduct our clinical trials, we are unable to directly control the timing, conduct, expense and quality of our clinical trials." (Wikinvest.com, 2009, p. 1)

So, perhaps our confidence in the quality of studies coming from CRO's should be questioned by our prescribing physicians.

But that circles back to our physicians not having all the data that they need to ask good questions. When the pharmaceutical company hires a CRO to do the testing, they routinely have contracts that: control the results, spin the results or even bury the

results. Drug companies may also provide “ghost writers” for articles submitted for publication; so, the independence you expect from articles may be lacking.

Celebrex and Vioxx are drugs you’ve likely heard advertised or perhaps you’ve even used one of them yourself. You might remember Olympic figure skater Dorothy Hamill being able to skate despite her arthritis pain. They were arthritis drugs which worked differently than the class of anti-inflammatories already marketed and were sales blockbusters. Celebrex had $3 B in sales over two years; Vioxx had $2 B in sales in less than two years.

A *Journal of the American Medical Association* editorial published in 1999 stated neither of these new drugs was better than naproxen which was already being sold for arthritis pain. You know naproxen as Aleve.

The hope was that Celebrex and Vioxx would be advantageous to the patient by preventing stomach upset. However, in 2001, the manufacturer of Celebrex had to issue a warning mandated by the FDA stating:

“...promotional statements and actions by or on behalf of Pharmacia (concerning Celebrex) to be false or misleading and therefore in violation of the Federal Food, Drug, and Cosmetic Act.” (Abramson, 2005, p. 23)

In the book *Overdo$ed America*, the author highlights a *New England Journal of Medicine* review article about Vioxx which said patients who took it experienced:

“twice as many heart attacks, strokes, and cardiovascular deaths and four times as many heart attacks as the people who took naproxen...” (p. 26)

How could that data have been missed in the original research? Perhaps a too short trial is the answer. An experiment that ended before the adverse reactions had time to appear.

And adding insult to injury, Vioxx cost about $117/month and over-the-counter naproxen costs about $7.50/month. So, not only were Vioxx and Celebrex NOT better than what was already on the market, they were more costly and had more side effects. Now that’s ugly.

Drug companies expand profits when they expand the market which is easily illustrated by the panel who looked at blood pressure. For years, hypertension or high blood pressure was defined as a blood pressure greater than 140 over 90. But when US guidelines on blood pressure were refined in 2003 and a blood pressure greater than 120 over 80 was termed “prehypertension” many more people needed medication. Of course, this population should first try to reduce their hypertension by lifestyle changes, but you are probably well aware how successful and well accepted that advice is in the US.

We should also be aware that if a drug ceases being profitable, the drug will stop being manufactured, regardless of the drug's efficacy. I suspect that is true in businesses in which some of you in this room are involved. It only makes sense to stop a non-profitable division or practice. But in the case of a valued drug, some of us would be more critical of that practice.

But, enough about the ugly; let's move along to the merely BAD.

THE BAD

Speaking of the FDA, when the latest guidelines were written on cholesterol, eight of the nine experts writing the guidelines were paid by drug companies either as speakers, consultants or their own researchers. Hardly sounds independent. *Selling Sickness* explains it is not unique to the subject of cholesterol but this is how guideline revisions work on most health issues in the US.

Costs of drugs is or should be concerning to all of us. What goes into drug pricing? Do drug prices reflect research and development? One source suggests the pharmaceutical industry spends more on marketing than it does on R & D. But, as I think of selling food or a gym shoe, I imagine that the 2:1 ratio is not so strange. While hard to confirm, several sources quote the figure of bringing a new drug to market, as costing $1B and 10 years of research.

What is also concerning and bad is what Congress did with Medicare which affects what all of us are paying for our own prescriptions. As you business owners buy health insurance and drug coverage for your employees, you are probably negotiating price breaks. Congress passed legislation <u>prohibiting</u> Medicare from negotiating lower drug prices. When you consider how many times each of us is paying for that piece of legislation, most of us would agree, that was <u>very</u> bad.

I recently heard a man at Walgreens complaining to the pharmacist about the cost of Viagra. "$10 a pill? That's outrageous!" His wife standing behind him said, "Go ahead and pay it, dear. What's $30 per year to us?"

Speaking of drug prices, let me tell you about ALLHAT. A-L-L-H-A-T. ALLHAT is the acronym for the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial. This was an 8 year multi-center study looking at 42,000 subjects over the age of 55. The study was a randomized controlled study that we earlier described as the gold standard in research. One of the study's goals was to determine what was the best drug treatment for high blood pressure. Four drugs were evaluated: calcium-channel blockers, alpha-adrenergic blockers, ACE inhibitors and a generic diuretic or water pill.

Results published in *Journal of the American Medical Association* in 2002 revealed that the most effective drug was also the cheapest and the oldest. The water pill won.. But is that what patients request from their doctor's? The average American sees nine TV

commercials each day for drugs and I'd say it's pretty unlikely that a generic water pill is one of them.

And, not to get too personal, but do you ever find yourself talking excessively? Not listening? Or being forgetful? I'm thinking all could be said about me, most days. These three descriptors are phrases from the *Diagnostic and Statistical Manual of Mental Disorders* defining attention deficit disorder (ADD). The authors of *Selling Sickness* describe this practice as "medicalizing" normal life. That's bad

Lilly advertises it's non-amphetamine drug for ADD by asking you the questions: distracted? disorganized? frustrated? modern life or adult attention deficit disorder? Who could reply in the negative?

Pediatrician Lawrence Diller is quoted in the book *Selling Sickness,*

"I began to wonder if boyhood, at least in my community, had become a disease." (p.76)

Since the market for ADD meds (like Ritalin) would likely be limited to children, expanding the market to include adults who talk too much, have trouble focusing and are often forgetful expands the ADD universe tremendously.

You might have noticed that we had an osteoporosis outbreak after the drug Fosamax was approved in the mid '90's. Its manufacturer, Merck, was ever so helpful in getting us to recognize the problem. It did so, in part, by subsidizing bone density testing machines for doctor's offices, machines necessary to get the diagnosis of osteoporosis.

And, if we would benefit by taking Fosamax in absolute terms, not relative terms, perhaps we have not been harmed. However, the practically free measure we could take to avoid a bone fracture, like improving our diet, increasing weight-bearing exercise and discarding those throw rugs, are ignored since there's a miracle drug claiming to correct your bone loss.

We know that advertising works. Direct-to-consumer advertising allowed in 1981 not only drove drug sales higher, it also helped us diagnose ourselves. A very unfortunate change. Caring celebrities and industry-sponsored advocacy groups through helpful ads increase the likelihood of us saying, "Gee, that sounds just like me. I am feeling a little tired, a little agitated. Perhaps mother's little helper is the answer."

Years ago, a woman with PMS self-medicated with chocolate covered pretzels but today she might be diagnosed with PMDD, premenstrual dysphoric disorder. Eli Lilly took its antidepressant drug Prozac, changed it's outside to pink and purple, re-named it Serafem and invented a new drug for PMDD.

Dr. Paula Caplan a Brown University professor challenges even the diagnosis of PMDD, stating:

"the condition has essentially been invented, and there is no strong scientific evidence to distinguish it from normal premenstrual difficulties." (Angell, 2005, p. 76)

In, *The Truth About the Drug Companies*, the former editor of the *New England Journal of Medicine*, Dr. Marcia Angell stated:

"Once upon a time, drug companies promoted drugs to treat disease. Now it is often the opposite. They promote diseases to fit their drugs" (p. 88)

And speaking of purple pills, AstraZeneca's patent on Prilosec, an acid-blocker for gastroesophageal reflux disease, GERD, was expiring but they had another drug patented to take its place. So, trials were conducted to show their new, pill Nexium, was superior to their old pill Prilosec. Of course, this trial compared two differing doses of the two pills. Not surprisingly, the price of Nexium was eight times that of Prilosec which would, after the patent expiration, be sold over-the-counter.

There are numerous emotionally scathing articles written about excessive profits by drug companies which might be filed under our "bad" label as well. But who defines the word excessive? Isn't any company's goal to sell their product? "Excessive profits" might be a topic for another Quester.

While most of us here may not be qualified to do drug research, we do all understand that using too few subjects can skew the results and underreport important side effects and undesirable outcomes. This is one way a company might manipulate its data. Here's another.

In *Selling Sickness*, the authors posed two questions that I'll now ask of you:
1) Would you take a drug every day for five years if it lowered your chance of having a heart attack by 33 percent?
2) Would you be willing to take a drug every day for five years if it lowered your chance of having a heart attack by 1 percent?

Have you already guessed that these two questions are the same question expressed in two ways? One can present statistics in different ways to push potential patients into taking a prescription. By inflating the benefits stating relative risks instead of absolute risks.

So, that decrease from 3 percent to 2 percent IS a 33 percent drop in relative terms but only a 1 percent drop in absolute terms. You can imagine how authors present drug trial results when they are paid by the drug manufacturer. That's bad.

On the issue of PATENTS, attorneys in the room can attest, that they are invaluable in protecting the rights and profits of the innovator for his or her product. The pharmaceutical industry seems to have such an excellent handle on the value of patents (which currently extends a 20 year period from the time of application) that

instead of innovating these days, drug companies spend their time trying to extend their exclusivity through what is termed “me too” drugs.

“Me too” drugs seem to be almost identical compared to the original drug - a left handed version of a drug now sold as a right handed version of that same drug is one example. Changing the formulation from liquid to pill form allows for patent extension as well. The drug is different enough to qualify for a new patent protecting the drug, its pricing and its profit.

Why is this happening? Several authors feel the FDA, the chief regulator of our drugs, is at fault. The authors of *Selling Sickness* believe part of the problem is that the FDA is financed by drug companies and then, frankly, managed by them.

A 2001 issue of *The Lancet*, a well regarded British medical journal described our FDA as:

“a place where dissenting scientific opinion was suppressed and it had become a servant of industry.” (p. 166)

So, the organization with oversight wasn’t doing its job. Where have we heard that happen amongst governmental agencies before?

The FDA works with 18 advisory committees who make recommendations for drug approvals. Who serves on these committees? Outside experts who, unfortunately, may have financial gain from the approval. Over a two year period, the FDA granted 800 waivers to their own rules on conflicts of interest. They also allow their consultants to make up to $50,000 annually without having to declare the relationship.

The bad might also include the on-going story of GlaxoSmithKline who is accused of bribing doctors in China with speaking fees, cash payouts, extravagant dinners and all expenses paid trips. Chinese doctors are being encouraged to use Glaxo’s drugs in unauthorized ways. This follows on the heels of Glaxo paying billions of dollars to settle suits in the US for marketing malfeasance.

Bristol-Myers Squibb and Pfizer had to delay the release of a blood thinner they hope will supplant warfarin; approval was recently held up by the FDA. The FDA complained of altered records, ignored serious side effects and wrong medication being used in some of their trials. One of those testing sites gave 9000 patients the wrong drug or the wrong dose. There is no way to sugar coat that bad pill.

Bad might describe Lilly’s report last month that they would likely NOT make their 2014 revenue goals. They attribute this to losing the patent protection to Zyprexa in 2011 and losing the patent to Cymbalta at the end of this year. Also, last month, Merck announced it is cutting their workforce secondary to lowered reimbursement rates, generic competition and research dead ends.

Despite the ugly and the bad, there is much good to say about the drug industry.

THE GOOD

One “good” area of the pharmaceutical industry includes orphan drugs. In 1983, guidelines for this unique group of drugs was signed into law. Orphan drugs are intended for use in orphan diseases which, by definition, affect 200,000 or fewer Americans. Because potential profit would be limited, one could expect that the pharmaceutical industry to NOT be interested in pursuing the development of drugs for rare diseases. The government incentivizes these drugs with marketing exclusivity, tax breaks, government grant funding, and also waives FDA fees and the like.

Since passage of the law, drug approval rates are high; it is a $50 billion industry which accounts for 22 percent of drug sales. Novartis is the number one company in this segment. Conditions that are included in this group are Huntington’s Disease, ALS (Lou Gehrig’s disease) and muscular dystrophy. With the favorable financial climate, orphan drug development is expected to remain robust.

While there is much written about how few drugs are in the R & D pipeline of big pharma perhaps it’s not a critical issue; the trend for several years is that the big drug companies purchase innovative start ups when they show a new drug with great potential. Again, a strategy that industries like technology has been using for years.

Last month I heard Gilead Sciences bought a company that they believed developed a drug with a 100 percent cure rate for hepatitis C. It is currently being reviewed by the FDA and EU drug approval boards. Gilead, by the way, paid $11B for the company.

Some very good news about some specific drugs in the last 15 years include Gleevec made by Novartis; it is used to treat and cure certain types of leukemia. Testicular cancer is thought to be 96 percent curable today with combination drugs like bleomycin, cisplatin and etoposide. Hodgkin’s lymphoma has become another very curable cancer through a combination of drugs.

Vaccines are another good industry story. To take one example, polio vaccines, resulting from the work of Jonas Salk and Albert Sabin, has essentially eradicated polio. Only 223 cases worldwide were diagnosed in 2012; the vaccines are made and distributed by Aventis Pasteur and GlaxoSmithKline. Vaccines can eliminate chicken pox, diptheria, malaria and measles.

I think it is also good that the NIH has increased funding for research in the areas of cancer, diabetes and neurosciences which includes Parkinson’s and Alzheimer's disease.

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To conclude, the US pharmaceutical industry is big, robust and doing what it can to be profitable, mostly within the law. But, if it is to become totally legitimate, the laws and regulations already on the books will need some independent oversight.

One alternative solution to the problems we've identified today, as this nutrition professional likes to say, is to change our lifestyle so we become less dependent upon drugs. We know that a change in diet and exercise can improve blood pressure, cholesterol and blood sugar. But as Margaret Mead once said:

"Easier to change a man's religion than to change his diet."

If this paper didn't make you question your own prescription habits, but merely gave you a headache, take two placebos and call your doctor in the morning. Thank you.

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