

Medicine and The Pharmaceutical Industry: What's Right, What's Wrong, and What's to Come*

S Y Tan

**Adapted from the keynote address, "The Medical Profession and The Pharmaceutical Industry", SMA Ethics Convention, October 26, 1997.*

BACKGROUND

The US pharmaceutical industry, the prime producer of therapeutic drugs in the world, consists of some 100 companies with total annual sales of US\$58 billion. These companies, together with their counterparts in Europe and Japan, have given us numerous drugs that dramatically improve the quality of our lives. Drugs such as insulin, antibiotics, anti-hypertensives, non-steroidal anti-inflammatory drugs, and so on. And newly released drugs, seemingly on a weekly basis, promise effective relief for conditions as disparate as osteoporosis, AIDS, baldness, and even impotence.

The US spends over a trillion healthcare dollars annually, some 8.4% going for prescription drugs. To ensure that drugs and medical devices (as well as food and cosmetics) are safe, effective and honestly labelled, the US Food and Drug Administration (FDA) was established in 1931. A consumer protection agency, the FDA regulates a trillion dollars worth of products, and employs 9,000, including 1,100 investigators. Its approval process, criticized for slowness, insists on adequate and well-controlled trials. It also monitors approved-drugs through post-marketing surveillance, centering on a program called MedWatch, a medical product reporting program, which emphasizes the responsibility of healthcare providers to identify and report adverse events. Added warnings (eg liver dysfunction from the latest anti-diabetic drug, Rezulin) or outright recall (eg the weight-reducing drug, Redux) then follow.

In its unending quest for newer and better drugs, the pharmaceutical industry invests heavily in research and development. For 10,000 substances examined, only 20 enter animal studies, 10 enter human trials, and one gains final approval for human use. On the average, it takes 12 years and US\$231 million to bring one drug successfully to market. This high-cost, high-risk nature of drug development is the main reason why prescription drugs are so expensive. For example, measles, mumps, and rubella vaccines cost about US\$100 million annually. But such preventive measures curb these contagious childhood infections, which would otherwise have cost US\$1.4 billion, or 14 times the price of the vaccines. No one can seriously doubt that the pharmaceutical industry has been a beneficial partner in Medicine's fight against disease.

Those dependent on prescription drugs know how expensive their pills cost, and they must often wonder if these drugs are unjustly priced, since a virtual monopoly exists for many of them. Consider some examples (a month's supply) at a typical retail pharmacy in Honolulu: 0.625 mg Premarin, US\$24.20; 150 mg bid Zantac, US\$119.05; 60 mg Procardia-XL, US\$81.80; 20 mg Prozac, US\$87.05. Many patients, especially the elderly, depend on half a dozen or more different drugs on a regular chronic basis. Their annual medication tab – thousands of dollars in some cases – is mostly paid out-of-pocket rather than insurance-reimbursed.

It is not surprising that drugs would be costly given the long and tedious course towards approval, and the liability and uncertainty that can still follow. Just the same, drug prices have been escalating in the 1980s and early 90s, to consistently exceed the inflation rate. This has led to allegations of price-gouging and unconscionable profits by the pharmaceutical industry, which has indeed chalked up better than average returns on its investments. In response, the pharmaceuticals point to the increasing risk and cost of research, and the limited period of patent protection which averages 10 years. Nonetheless, they have recently instituted voluntary price restraints, and drug prices have stabilised.

How do we as physicians interact ethically with such an important and valuable partner that sells life-saving medications to our patients? As physicians, we are the exclusive authors of all drug prescriptions. We therefore have an interest in how much they cost, in using the most cost-effective preparations, and in avoiding undue influence by the manufacturers. In discharging our duty, we should be mindful that a pharmaceutical's business interest is in the preferential sale of its own products. Where then are the ethical pitfalls?

ETHICAL BREACH

I would like to divide my discussion of the areas of potential ethical breach into 4 categories: 1) Drug promotion; 2) Drug-sponsored continuing medical education (CME) programs; 3) Drug-sponsored research, and 4) The office dispensary.

I. Drug Promotion

Would you believe that some US\$10 billion per year are spent by the pharmaceuticals to promote their drugs? They do an impressive job with advertisements and "detailing" by trained professionals called drug-

University of Hawaii
John A Burns School
of Medicine
Honolulu, Hawaii, USA

S Y Tan, MD, JD, FACP
Professor of Medicine,
Professor of Law

reps. The promotion objective is to influence, using tested marketing strategies, the prescribing of a certain drug. And the centerpiece of drug promotion is the drug-rep, carefully selected for strong interpersonal skills rather than scientific prowess. After an initial training period at headquarters, they are released into the community, each with his/her own territory. They come to the doctor's office, or the hospital, to promote a new drug or a new indication, to tout a price reduction, or to neutralize a competitor's claims. I have always been charmed by their friendliness, confidence and unflinching service.

Drug-reps are neither physicians nor scientists, yet they impress us with apparent knowledge of their products. I have heard doctors say that drug-rep visits are an important source of their ongoing medical education. This is a pity, since learning about new drugs should come from unbiased sources such as "The Medical Letter." Drug promotions are self-serving, directed towards sales, not science. After all, the material being presented is necessarily one-sided, meant to influence, and presented by a non-expert.

In addition to their rehearsed presentations, drug-reps come armed with samples, presumably to benefit our patients. Say you offer the samples to a patient about to start on a new drug. After a couple of days without experiencing adverse effects, the patient then fills the prescription and buys the entire 2 weeks' supply, or a month's supply. That's a clear benefit to the patient who might otherwise be stuck with a full prescription that is either ineffective or to which he is allergic. For a poor patient, you might even provide the entire 3-day course of Bactrim from your sample closet to treat a UTI. Another clear patient benefit.

But like most good things, samples can be abused. An occasional doctor would actually sell these samples to his unsuspecting patients for personal gain. That has to be clearly unethical. What about many of us who regularly use these samples for ourselves or family members? About a third of drug samples are thought to end up this way. Ultimately, patients are the ones who pay, as the companies merely factor in these expenses when pricing their drugs.

Promotional gifts accompany the drug-reps on their rounds. Coffee mugs, pens and memo pads are favourites. Sometimes the offer is more tempting, eg, an all-expense paid trip. We need to ask ourselves where the permissible line is. The value of the gift is one factor, the benefit to patients another. Words like incentive, enticement and inducement should automatically raise our professional consciousness.

Drug promotions in all forms cost money, which is ultimately borne by patients. The doctor, sitting in the middle of these marketing ploys, can play an important role in ensuring reasonableness and maximum patient benefit. If we put our patients first at all times, if patient welfare is always paramount, we should be able to steer clear of ethical lapses. Here are 4 questions we can use to remind ourselves:

- 1) Will we be embarrassed if our patients found out?
- 2) Do the gifts primarily entail a benefit to patients?
- 3) Are they of substantial value?
- 4) Are there strings attached?

2. Drug-Sponsored CME Programs

The industry has always played an important role in providing CME programs for physicians. In 1988, 16 companies spent US\$85.9 million sponsoring almost 35,000 symposia across the US. An estimated US\$200 million is spent annually on educational program sponsorships. Although physicians must feel privileged that someone else is paying for their ongoing medical education, surely an outsider must wonder why a highly paid profession like ours should enjoy a benefit that raises issues of ethics and propriety.

Promotional efforts can be couched in educational terms, the better to influence the uncritical physician. It is not always easy to tell promotion from education. And attractive incentives such as a resort excursion for a "CME program" can sometimes cloud the physician's judgment. Notwithstanding protests that we are not so easily influenced, physicians indeed have been shown to significantly favour the prescribing of specific drugs promoted at such conferences. In one follow-up study, physicians from targeted medical centers wrote 10 times as many prescriptions for the company's product after they returned from a CME-excursion to a Florida resort.

Education's goal is to offer unbiased scientific information, highlighting both the salutary as well as the adverse or unknown effects of the drug, so that the practitioner can become more knowledgeable about the disease process and its treatment. At the minimum, we should insist on the impartiality of the speaker. In the US, strict guidelines govern programs that are being offered by pharmaceuticals if the attendees are to receive CME credit points towards re-licensure. These guidelines mandate the disclosure of conflicts of interest (the speaker signs a form stating whether he has a direct financial interest in the company), and require a clear statement in conference announcements of the source of sponsorship. Evaluation forms must specifically seek feedback on possible bias in the presentation. Most importantly, the content and choice of speaker rest exclusively with the CME organising committee rather than the sponsoring company.

Drug-sponsored programs are here to stay. The best protection for our patients is to minimise the receipt and use of biased information. Teach our physicians to develop a critical scientific mind, one that demands evidence-based medicine. Remind ourselves that all presentations are subject to scrutiny; those sponsored by the industry more so.

3. Drug-Sponsored Research

We can expect accelerating research collaboration between academia and industry with the perpetual threat of shrinking government research funds. There is nothing intrinsically improper with such collaboration. Financial support by the pharmaceutical companies can lead to useful research that can ultimately benefit mankind. The overriding ethical issue is to ensure the complete independence of the researcher. This includes allowing the publication of relevant research data free of all interference, subject only to the usual journal peer-review. Thus, the

supporting agency must bear the risk of unfavourable results. Restrictive covenants serve to jeopardise the scientific objectivity of the investigator, and ultimately hurts the consumer. A recent Californian scandal involving studies on thyroxin bioequivalence is a case in point, with litigation leading to a multi-million dollar settlement. As in all other human studies, full informed consent to protect experimental subjects is paramount, and disclosure of sources of grant support should accompany all verbal or written presentations.

What about incentives for participating in drug-sponsored research? A small token of appreciation to the research subjects, eg, meal tickets at the hospital, are acceptable. They are unlikely to unduly persuade or coerce participation in the drug trial. Likewise, a thank you gesture such as a medical text to encourage personnel to enlist patients in an approved drug-trial (with Institutional Review Board approval and informed consent, naturally) is not unethical. Again, the intent here is to remind and encourage medical personnel to enroll subjects so as to ensure the success of the experiment, which can ultimately benefit patients.

4. The Office Dispensary

The ethical issue surrounding operating an office dispensary continues to generate controversy. A dispensary can be a good idea if it serves the patient's best interest – providing convenience, competitive-pricing and relevant patient education. Not so if the office dispensary is exploitative. One should not be selling medications at inflated prices to one's own patients just because they represent a "captive audience"; or allow medication charges to be commingled with those of the office-visit. Properly itemised, the charges for drugs can then be compared with those of the pharmacy down the road. This gives the patient the genuine option of filling his prescriptions elsewhere.

The office dispensary should meet or exceed community pharmacy standards in areas such as purchasing, storage, labelling, warnings, education, and so on. Samples do not belong in the dispensary. If possible, avoid charging your patients more than the retail pharmacy. Your office dispensary is to provide convenience and education for your patients, not to generate additional substantial profits.

Be circumspect over incentives that the pharmaceuticals may offer you on certain drugs. Such incentives immediately risk their preferential prescribing for greater profit, and make overtake your better medical judgment. To avoid this conflict of interest, charge, on all drugs, a fixed percent or dollar premium over cost.

AN ABC ANALYSIS

One way to work through these ethical issues is to use what I have termed the ABC approach. The mnemonic stands for:

Appearance of impropriety;
Benefit (to patients), and
Cost.

The emphasis is on the appearance of, rather than actual, impropriety itself. It should require little reflection to avoid something that is improper or illegal. But the conduct doesn't have to be improper, so long as it looks improper to our patients and to our colleagues. As medical professionals, we are accorded a special position of stature, respect and trust by society. What it observes and concludes as unprofessional or unethical conduct is likely to tarnish the individual as well as the entire profession. Our explanations or rationalisations may not be understood; besides, we may not have the chance to explain our actions. If it smells bad, keep your distance. Call this the "nose test".

Incidentally, a study of patient attitudes regarding professional propriety revealed the following approval rates: dinner, 34.6%; cocktail party, 44.5%; pens, 67.3%; medical books, 70%; and samples, 82.1%.

All drug-related activities should benefit patients in an easily recognisable way. The question to ask is: Does it entail a benefit to the patient? Say you are invited to a conference. A modest lunch is provided, and the drug-sponsored speaker is updating the treatment of diabetes. Various drugs are mentioned, including side effects, pros and cons, and price comparisons. The presentation is scholarly and objective, and there is full disclosure of sponsorship. You upgrade your medical knowledge, and return to the office better able to treat your diabetic patients. The luncheon conference has produced a direct patient benefit. There is no overt or hidden incentive, no lavish entertainment, no discernible bias. In short, no appearance of impropriety. The cost (lunch, speaker honorarium, handouts, room rental ... etc) is manageable and reasonable. This scenario passes the ABC test. It is ethical.

Sometimes the benefit accrues instead to the doctor. For example, an expensive gift like a wristwatch. It looks wrong, there is no patient benefit, and the cost is excessive. This fails the ABC test and is unethical.

Another scenario – a true account of a recent event in Honolulu. A flyer circulates around the hospital inviting house-officers to enjoy "happy hour" after work on a Friday afternoon. Free drinks, snacks, karaoke, fun. You may contact one of three listed names in order to sign up. They are representatives of a pharmaceutical company, although the company itself is not identified by name. There is no CME program to be offered. Just a PR party. Can we reasonably assume that promotional pamphlets, perhaps small gifts, will be handed out? Does it not look improper? Benefit to patients – none. And at some indirect cost to them. This would fail the ABC test and be deemed unethical.

Since all activities incur a cost that is ultimately paid by the patient, we must carefully weigh this cost factor against patient benefit. A small medical textbook gift arguably helps the doctor take better care of the patient, whereas a set of golf balls does not. It would be easier to approve the former, not the latter.

TRENDS INTO THE MILLENNIUM

I wish now to discuss what I perceive to be four important drug trends as we enter the 21st century. These trends raise important ethical questions, and physicians will do well to prepare to face these challenges.

Trend 1: The Ubiquity of Direct Marketing

Direct consumer drug advertising expenditure has gone up from about US\$10 million in 1992 to an estimated US\$800 million in 1997. Pharmaceutical companies market their drugs directly to consumers in the newspapers, magazines, TV/radio, and the internet. Everywhere you look, you see ads shouting down at you regarding the best bet for your health. *Consumer Reports*, a US magazine, astutely wrote in its June '96 issue, "These are not public service messages. They are meant to move the goods."

It has been estimated that 90% of physicians are willing to write a prescription for a drug specifically requested by the patient. The industry knows this, and has embarked on an all-out advertising campaign to influence consumers on the choice of prescription drugs. Such ads are regulated by the FDA, whose rules require "fair balance", ie, that the ads objectively describe the benefits and risks, and include a brief summary of the side effects, contraindications and effectiveness. But this supervision has not always been effective, and may be weakened further by recent proposals to re-define "fair balance".

The public is supposed to understand these ads and decide prudently whether they should request a particular prescription drug. A review article recently examined pharmaceutical advertisements in medical journals. A group of impartial experts concluded that 28% of the ads should not appear at all, and 34% needed major revisions. These remarks pertain to ads targeting the medical profession whose members are said to favour ads over reading the medical literature because they are more "visually arresting" and "conceptually accessible." More reason, therefore, to believe that the lay person will be at greater risk of being misled?

But direct marketing may have its merits. Advertising has been called a legitimate expression of free speech which serves to educate the consumer. This leads to better health consciousness and therefore better doctor-patient communication. It promotes competition among the drug companies, thereby leading to lower drug prices. And it forces the doctor to keep up-to-date.

Most doctors are uncomfortable with direct drug marketing, believing that they, rather than the industry, should be providing the relevant information to patients. Some believe that advertising may drive up healthcare costs (debatable?). One saving grace: We doctors are still the ones with the ultimate authority and responsibility for writing the prescription – the final advocate to guide the enthusiastic, if unwary and gullible consumer.

Trend 2: The Preference for Generic Drugs

Generic drugs account for 60% of all prescriptions written in 1997, up from 20% in 1984. From 1991 to 1995, the dollar value of generics rose from US\$5.5 billion to US\$15 billion. Little appreciated is that 80% of generics are produced by brand-name pharmaceutical firms. Ten pioneer drugs lose their patent protection each year. This year, Zantac, Rogaine, Taxol and Platinol will go generic.

Generics do not have to go through clinical trials to show clinical efficacy, but like brand-name drugs, they remain under FDA regulation. The FDA approves about 250 generic drugs a year which must demonstrate bioequivalence, ie, within $\pm 20\%$ of serum drug levels achieved with the patented original. So one can theoretically see a 40% variation in serum drug levels, which poses a problem for drugs with narrow therapeutic windows. Worse yet if strict quality control is lacking.

Generics cost less, sometimes markedly so. For example, 100 tablets of Atarax cost US\$67.95, the generic version, US\$11.35. Likewise, Tolinase, a first generation sulfonylurea, costs US\$86.85 for a hundred tablets (500 mg), but only US\$25.95 for generic. Only a small difference, however, exists for some drugs such as thyroxin. Synthroid, the brand name, costs US\$12.85 (30 tablets) compared to US\$11.75 for generic.

A scandal affecting fraudulent generic drug testing some years ago threatened to reverse the trend towards generics, but this has not happened. Physicians can expect to see a rising emphasis on, and utilisation of generic drugs for reasons of cost and comparable efficacy in most instances. However, they must be vigilant against ineffective substitutes. And recognize that cardiovascular, anti-convulsant, psychotropic and sustained-release drugs are particularly apt to cause problems in their generic forms.

Trend 3: The Proliferation of Pharmacy Benefit Managers (PBMs)

PBMs are not people; they are companies belonging to a rapidly growing profitable business that manages pharmacy benefits (US\$45 billion annually). PBMs market competitively-priced drugs and pharmacy services to managed care organisations and other health plans. Knowledgeable about drug prices and utilisation, they offer advice regarding formularies, generics-promotion programs, physician education, drug utilisation reviews, and patient compliance management. In the near future, PBMs hope to actively orchestrate patient management via treatment guideline protocols. Overseeing some 60% of all retail drug prescriptions, PBMs directly influence the healthcare of 100 million Americans.

A PBM agent may call you on the phone and say: "Hey Doc, instead of using such and such a drug, can we substitute a generic which is equally efficacious and cheaper." Or there may be a suggestion for an entirely different drug, either in the same or different class. In some instances, informing rather than seeking the physician's approval is all that is required, especially

in healthcare plans with a closed and restrictive formulary. Worse yet, the switch may be made entirely without the doctor's knowledge.

Remember, drugs account for over 8% of healthcare expenses. PBMs can therefore be an important force in controlling health costs. Keenly aware of PBMs' important and growing role, the pharmaceutical industry has purchased some of the largest PBMs like Medco Containment Services, Diversified Pharmaceutical Services, and PCS Health Systems. They are now owned by Merck, SmithKline Beecham and Eli Lilly respectively, at a total purchase price of US\$10 billion. This staggering sum is roughly equivalent to bringing 40 major new drugs to market. The trend is clearly in the pharmaceutical's best business interest. Vertical integration breeds efficiency. After all, if you produce and manufacture the drugs, you might as well control their distribution, all the way down to the consumer. Especially if you are able to track and influence the physician's prescribing habits with cost-effectiveness and local clinical outcomes data.

The growth and integration of PBMs into the pharmaceutical industry raise anti-trust issues. Smaller players are at a disadvantage, and local pharmacies may be unable to compete. It harms R&D, the money being better used for research into new cures. Many have pointed to the inherent conflict of interest for a drug company to own a PBM. Predictably, abuses have occurred, at the expense of consumers. One such abuse – drug switching, to favour the pharmaceutical's own product. Another is the use of rebates to induce HMOs and insurers to use its brands. Such concerns have led the FDA to recently announce its intent to increase its scrutiny of drug-owned PBMs.

Trend 4: The Regulation of Alternative Medicine

In Singapore, we all grew up using various alternative forms of medicine such as Chinese herbal drugs and acupuncture. In the US, for the longest while, alternative medicine was frowned upon by the medical profession, and generally avoided by the public. No longer. A recent telephone survey revealed that 1 in 3 Americans use alternative medicine, with the frequent users being educated, upper-income whites, ages 25-49. The cost in 1990 was US\$13.7 billion. Importantly, most of those polled (72%) indicated that they did not tell their doctors they were using such forms of treatment.

These results have led to a re-examination of alternative (or complementary) medicine in the US. The National Institutes of Health established the

Office of Alternative medicine in 1991, and some medical schools are already including this subject in their formal curriculum. It is more than a passing fad. The proliferation of alternative modes of treatment, most of which remain scientifically unproved, has led one editor to remark in 1993 that, "The public's expensive romance with unconventional medicine is cause for our profession to worry."

Incredibly, much of alternative medicine in the US goes totally unregulated. Herbal preparations and dietary supplements are widely available "over the counter", without FDA oversight. Their use may be particularly dangerous in children and pregnant women. Ads have grown increasingly bolder, with unsubstantiated claims that overreach, even defraud. Melatonin has been claimed as cancer-preventing and life-extending – at US\$3.79 for 60 tablets. A recent newspaper ad in Honolulu promotes it as an immune system stimulator that helps lower cholesterol levels. The benefit, if any, of virtually all herbal preparations, is unknown. More ominously, actual harm has resulted from adulterated preparations which may contain ephedrine, mercury, or other harmful substances. Or the preparations themselves are intrinsically toxic, and deaths have occurred as a result.

Advocates of alternative medicine say that their drugs are natural and therefore safe, a manifestly illogical conclusion. They are claimed to be effective, proven by time if not by experimentation. Besides, practitioners of unconventional medicine may appear more caring and they devote more time listening to their patients. What is wrong with a placebo effect anyway, so long as the patient improves, they argue. Opponents, on the other hand, are particularly disturbed over the danger of delayed diagnosis and treatment, and complain that the unregulated use of alternative medicine promotes quackery and exploitation of the vulnerable patient in search of palliation or cure.

I tend to believe that some forms of unconventional treatment will eventually be proven to be beneficial. Many are probably worthless, and a few may be harmful. In the meantime, 3 proposals appear self-evident: First, doctors should familiarise themselves with this new and growing area, if only to understand their patients better and to possibly guide them in their choices. Second, there is an acute need for scientific research using, to the fullest extent possible, the randomized, placebo-controlled, double-blind clinical trial strategy. And third, it is time to judiciously regulate both the use and the advertisement of these products in order to safeguard our patients.