Perils of a lemon

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Donald W. Light, editor

THE RISKS OF PRESCRIPTION DRUGS

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Most of us are now aware to varying degrees that some pharmaceutical companies engage in a range of questionable strategies to promote their products, such as concealing unfavourable results, playing down side effects and "ghost writing" – paying academics to put their name to company-generated research. But we also believe that the drugs we get from our doctors have a solid evidence base, supporting their use. If they weren't safe and effective, they wouldn't be prescribed.

It's a contradictory position that we can generally ignore, since the proof tends to come from American court cases or is buried in specialist journals. Occasionally, pharmaceutical malpractice may be exposed by a media investigation, such as the BBC *Panorama* programme some years ago about the raised risk of suicide among children given antidepressant drugs, a risk the companies had long denied. Such cases are rarely described as being part of a wider problem. Instead they tend to be treated as unfortunate aberrations, a few bad apples in what is otherwise the essential health-giving, life-saving barrel of prescription drugs.

Donald W. Light, an American sociologist, does not agree. According to *The Risk of Prescription Drugs*, the problem is endemic. The drug regulatory system, supposedly designed to protect us, actually ensures a regular production of these "lemons" – products that are unsafe and largely ineffective. At first sight this seems absurd. What could be more tightly controlled than prescription drugs? Doctors today practise evidence-based medicine. We have elaborate systems of regulation. Companies have to run large and expensive trials involving hundreds if not thousands of patients, testing new drugs against a placebo to prove they are safe and effective before they are allowed to be prescribed.

Professor Light painstakingly demolishes this comforting belief. Shoppers in supermarkets or on the high street assume that any purchase does pretty much what it claims to do. More importantly, if it doesn't, you have the right to complain, return it, or be compensated, and there are penalties for sellers who try to pass off inferior or dangerous goods as genuine and safe. Such safeguards, claims Light, don't apply when it comes to our consumption of prescription drugs. When we take pills to stave off heart disease, reduce depression or control diabetes, the risk is on us. *Caveat emptor* rules. And the heart of the problem is an imbalance in information. Drug consumers shoulder the risk because it is the companies that hold all the information, which they can manipulate to their own advantage. Although prescribing is supposed to take place on a firm evidence base, all too often patients have to rely on trust. "Executive and marketers of pharmaceutical companies", writes Light, "have developed some of the most elaborate institutions of hope and magic in modern culture." It is the same charge that is regularly levelled at practitioners of complementary medicine. Can it be sustained?

To locate the source of the problem, Light homes in on the placebo-controlled trial, the cornerstone of evidence-based medicine. Rather than protecting patients, he alleges that it actually works to guarantee the production of "lemons". The requirement to test only against a placebo ensures that a high proportion of new drugs are no improvement on what is already available and are quite possibly more dangerous, but can be sold at higher prices.

From the corporations' point of view, this is a perfectly rational strategy. If you only have to show that your drug is better than a sugar pill, then you concentrate on developing easier "me too" drugs – ones that are similar to those already on the market but different enough to get a licence. Research carried out by the US Food and Drug Administration shows that between 1960 and 1979, only one drug in nine "provided superior therapeutic benefit". The figure improved slightly between 1981 and 2006, to one in seven. Even though a drug is similar, it may still come with a slightly different side-effect profile, but that won't become clear for a number of years.

It is a truism that all drugs have side effects, so the regulator has to perform a balancing act: the more serious the disorder, the more acceptable are severe side effects. A drug for arthritis has to be much safer than one for late-stage cancer. The formula commonly used to cover this is to say that the "benefits outweigh the risks". But Light sees this as another way of justifying the transfer of risk from the company to the patients. "The phrase sounds like a scientific evaluation or a mathematical exercise", he writes. "But there is no standard method; no scale exists that allows an objective comparison. It is a qualitative judgement made by experts based on available data that is largely generated and presented by the company."

Much of the book is taken up with itemizing the various ways in which drug companies can massage the data from trials to suit their own ends, and Light is not alone in pointing this out. Marcia Angell, a former editor of the *New England Journal of Medicine*, has covered similar territory in books and articles. What makes *The Risk of Prescription Drugs* a valuable addition to such critiques is that it locates the problem not in the behaviour of the companies, but within the regulatory system that makes their actions profitable and rational. And he makes a number of suggestions as to how the risk could be more evenly distributed and patients better protected. One would be to require that drugs be tested not against a placebo but against the best existing treatment. What patients and doctors want to know is not whether a treatment is better than "nothing" but whether it is better than what they have already.

Light's notion of "lemons" might be regarded as a hypothesis about the perverse incentives of the regulatory system. If so, it received impressive support from the events leading up to the recent withdrawal of the diabetes drug Avandia, described in another *Panorama* programme broadcast after the book was written. Avandia was launched a decade ago as a solution to diabetics' raised risk of heart attacks, but was found to increase it.

A trial to test the possible link with heart attacks was commissioned at the same time as the drug was licensed, and took nine years to report. It was entirely controlled by the company, and found no added risk. Subsequent detailed analysis of the raw data of the trial raised serious concerns that the findings were unreliable. The programme revealed that other company-run trials had found evidence of the heart-attack danger but that these had not been made public until an independent investigator found them. Each of these actions had the effect of pushing risk on to patients. Shifting risk in this way is only possible because drug companies generate and control most of the information used to make decisions about drugs, and it is not just scholars such as Light who are concerned. Responding to the Avandia saga in the *Panorama* programme, Dr Fiona Godlee, Editor of the *British Medical Journal*, remarked:

> Even the most loyal Manchester United fans do not expect Alex Ferguson to referee a match. At the moment we have got the industry controlling the design of the studies, controlling the data and controlling the reporting of those studies and it is just not acceptable.