nature medicine

When true enough is not good enough

A recent court ruling that favored freedom of speech over the authority of the US Food and Drug Administration (FDA) to regulate off-label drug promotion may have profound implications for the way drugs are marketed and, ultimately, for patients' interests.

The off-label use of medications is exceedingly widespread and accepted by the medical community. Physicians can prescribe any approved drug for any condition they choose and discuss off-label use with their colleagues, and patients are certainly free to take drugs off label.

In fact, virtually anyone who doesn't work for the pharmaceutical industry can advocate for the off-label use of a medicine. Under the Food, Drug and Cosmetic Act (FDCA), which gives the FDA its regulatory authority, it is a crime to promote a drug for purposes not listed in its label. In FDCA language, "introducing a misbranded drug into interstate commerce" is illegal. GlaxoSmithKline's $3 billion settlement last summer for promoting Avandia and other drugs for unapproved uses is a stern reminder that the FDCA means business.

But on 3 December, a federal appeals court changed the status quo by overturning the conviction of Alfred Caronia, a sales representative for Orphan Medical, who promoted a drug for uses not approved by the FDA. The case involved the drug Xyrem, the active ingredient of which is γ-hydroxybutryate, a compound federally classified as the 'date rape drug'. Xyrem is prescribed for certain types of narcolepsy, but Caronia was caught promoting the drug for patients with conditions as diverse as fibromyalgia, restless legs syndrome, chronic pain and Parkinson's disease.

In a 2-to-1 decision, the judges stated that banning off-label marketing violated the representative's freedom of speech. This ruling is a mistake, as it upholds the freedom of speech of people with a vested interest in promoting a product without considering the risk this represents for patients. By opening the door to off-label drug promotion by people with commercial motivations, the court decision undermines the authority of the FDA and the process whereby new drugs are approved. Indeed, the dissenting judge, Judge Debra Ann Livingston, argued that if pharma companies can promote FDA-approved drugs for nonapproved uses, "they would have little incentive to seek FDA approval for those uses." In other words, why bother with a long and expensive clinical trial if one can just market a drug without it?

The court found that, as long as the information that pharma sales representatives give to doctors is true, the FDCA cannot curtail their freedom of speech. The decision therefore changes the burden of proof for prosecution of companies for misbranding a drug in accordance with the FDCA. It will no longer be enough to spot off-label marketing to cry foul; instead, it will be necessary to show that the information presented is false. But, considering that there are essentially no clinical efficacy data for using Xyrem to treat Caronia's broad list of diseases, the ruling did not seem to take into account whether his statements were true or not. For the purpose of the decision, they seem to have been considered as true enough.

The FDA is likely to appeal the decision, which may find its way to the US Supreme Court, where it will hopefully be reversed. But if it isn't, and off-label promotion prevails, how will the validity of claims of drug efficacy by evaluated? To regulate the promotion of over-the-counter products, the US government uses the Federal Trade Commission (FTC) Act, which also requires experimental evidence of efficacy before any claim about the properties of a product can be stated to consumers. But it is easy to see from the countless 'dietary supplements' in the market that the burden of proof for the FTC is very different from the current drug-approval system enforced by the FDA.

All parties—government, companies, physicians and patients—agree that off-label use of a drug has a legitimate place in the practice of medicine, provided it rests on truthful, scientifically accurate information. The current system aims to balance between giving doctors the authority to prescribe drugs as they see fit and giving the FDA a clear-cut standard by which to keep the marketing departments of drug companies from running amok. Allowing companies to market drugs for unapproved uses will compromise the principle that drug efficacy should be determined by rigorous clinical trial data and will result in drugs being used inappropriately, which can harm patients. When it comes to patients' interests, the government and the pharma industry should not start playing games trying to agree on what reliable scientific data are, because 'true enough' is simply not good enough.