

Opinion

Off-Label Drug Use: Is Regulation Internationally Contagious?

The Oct. 4, 2012, *New England Journal of Medicine* contained a perspective (pages 1279-1281) that was easy to overlook, as it was bookended by the seductive titles “Mydriasis in the Garden” and “Mites in the External Auditory Canal.” The subject was the new law in France that curtails the legal use of off-label medications in the name of safety. But to my ear, it sounded the clarion that the freedom U.S. physicians have had in using medications off label is at risk, if international regulation is catching.

According to 12-year-old data, about 20 percent (150 million) of U.S. prescriptions are for off-label uses,¹ so it’s a prevalent practice. The situation that galvanized the French to pass their new law was the widespread use of benfluorex, a fenfluramine derivative approved for treating diabetes but often prescribed off label for obesity, resulting in a rash of cases of fatal cardiac valvular disease. Such cases have occurred in the United States, of course, but to date the FDA has not outlawed off-label use. I don’t claim to be an expert in drug regulation, so I thought it might be instructive to include several quotes from the *NEJM* article to leave you with the spirit of French thinking on the subject and (in parenthetical comments) why I am alarmed about it.

“Some off-label prescribing should be permitted to allow physicians to take good care of patients and offer

them some therapeutic options, but such prescriptions must remain the exception to the rule and should be scrutinized and controlled by regulatory agencies using well-defined frameworks.” (How long will this take, and who will pay?) “A TRU (temporary permit) is granted for a maximum of 3 years, a window that should permit the manufacturer to expand its marketing authorization through the usual procedures.” (At a few million euros per indication.) “Several factors must be considered and carefully balanced by an expert committee before a TRU can be issued. The first is the quality of the scientific evidence. ... The second factor is the drug’s safety. ... Third, the prognosis associated with a given disease must be considered. ... For this reason, TRUs will probably be used most often in oncology and hematology, followed by infectious diseases.” (Sounds like ophthalmic indications are out.) “The fourth consideration is the frequency of the disease’s occurrence.” (The rarer the better for chances of a TRU approval.)

Off-label prescribing is a privilege worth retaining. When approved treatments have failed, drugs used off label can offer an important alternative to the patient. The emergence of new data allows physicians to adopt new evidence-based practices. Of course, doctors might prescribe off-label medications that have proved to be useless or even harmful in treatment of a given

condition. The off-label privilege is a double-edged sword.

I recently attended a talk on stem cell therapy in ocular diseases. With the appropriate growth factors and gene regulators, skin fibroblasts or blood cells can become retinal pigment epithelial cells, photoreceptors, and ganglion cells. Modulatory drugs are needed, and they may well come from the vast library of approved drugs. If they cannot be used off label for this research, human trials will be set back years to decades. Let’s hope the French regulations aren’t contagious.

1 Radley DC et al. *Arch Intern Med.* 2006; 166(9):1021-1026.



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