CORRESPONDENCE

Off-Label Use of Drugs and Devices

EDITOR:

IN THEIR EDITORIAL "WHEN IS OFF-LABEL DRUG USE IN the Patient's Best Interest?,"[1] Rosenfeld and Goodman raise ethical questions about the off-label use of intravitreal Infliximab to treat neovascular age-related macular degeneration by Theodossiadis and associates.[2] Rosenfeld and Goodman confuse *unproven* with *off-label*. They say that "patients had not failed ranibizumab therapy when the decision was made to change them from an approved drug to an *unproven off-label* drug" (italics added). Later they ask whether "Theodossiadis and associates violate[d] international standards by performing *off-label* Infliximab injections?" (italics added) and stated that off-label treatments must be preceded by a "robust consent process."

A drug or device becomes "on-label," or approved, when a sponsor conducts a prospective multicenter clinical trial to show its safety and efficacy for a particular indication. Often these regulatory trials are of limited value, for several reasons. First, often the approved indication is of little value, whereas off-label indications are the primary use. Manufacturers often take the most direct route to an approval rather than demonstrating the best use of the product in a clinical trial. For example, topical ophthalmic antibiotics universally are approved only for the treatment of bacterial conjunctivitis, a self-limited condition with little morbidity. However, their greatest value is in the treatment of bacterial keratitis and in prophylaxis after ophthalmic surgery. These applications are *proven* off-label uses. The use of these agents is entirely ethical. To my knowledge, not a physician in the world has a "robust consent process" (or in fact any consent process) to explain the off-label use of topical antibiotics after surgery or to treat bacterial keratitis.

Second, often regulatory trials are not designed to provide useful information. For example, all of the wavefront-guided excimer lasers were approved in Food and Drug Administration (FDA) trials that did not compare them with the prior non–wavefront-guided lasers, but rather with absolute standards of efficacy and safety. In deciding whether to recommend wavefront-guided treatment to their patients, physicians rely on non-FDA trials to make those recommendations.

Third, sometimes regulatory trials are simply wrong. Intacs intracorneal segments were approved as a safe and effective treatment for myopia by the FDA. Physicians abandoned their use because they were not effective (they were inaccurate and caused induced astigmatism) and not safe (they caused complications such as corneal erosions). This is an example of a treatment that is approved but *proven ineffective*.

Treatments become approved only if there is profit to be had in the treatment. Because of the vast costs of FDA trials, manufacturers do not undertake to sponsor regulatory trials unless they can make money selling the device or drug involved. As a result, many of our most effective treatments are not FDA approved because they are not associated with high-profit drugs or devices. Trabeculectomy, extracapsular cataract extraction, scleral buckling, appendectomy, and coronary bypass grafting are vision-saving and life-saving treatments that are not FDA approved, but certainly are the standard of care for their respective conditions. Surely Rosenfeld and Goodman would not claim that a "robust consent process" for their nonapproved status should precede their use.

Suggesting that off-label treatment requires a special consent process is tantamount to saying that patients should be informed of the ability of a for-profit company to make money selling a device or drug. This is (fortunately) largely irrelevant to the consent process. What matters are the risks and benefits, and how well those risks and benefits are known. The specific regulatory status of a device or drug is largely irrelevant to the ethics of medical treatment. A robust consent process is appropriate for unproven therapies, but rarely is indicated simply because of the labeling of a device or drug in a particular jurisdiction.

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REFERENCES

1. Rosenfeld PJ, Goodman KW. When is off-label drug use in the patient's best interest? [editorial] Am J Ophthalmol 2009;147: 761–763.
2. Theodossiadis PG, Liarakos VS, Sfikakis PP, Vergados IA, Theodossiadis GP. Intravitreal administration of the anti-tumor necrosis factor agent infliximab for neovascular age-related macular degeneration. Am J Ophthalmol 2009; 147:825–830.

REPLY

WE READ THE LETTER FROM DR MALONEY WITH GREAT interest and wholeheartedly agree that the off-label use of drugs and devices is appropriate in routine clinical practice. If he assumed that we held a different position, then

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