label (221), or a combination of drugs that is not on the label (222).

Populations that are commonly underserved by FDA-approved medicines include cancer patients, children, and pregnant women (223). For many cancers, such as rare tumors, there may never be enough evidence to support a labeling indication because of the inability to conduct the appropriate trial as a result of inadequate patient numbers (224). Another factor that impairs the ability to recruit subjects for off-label uses is as follows. Patients are reluctant to participate in a randomization process that only provides investigational treatment to some patients, especially when the drug is already widely available (225).

Cost is another factor that encourages off-label use. This example is for antibody drugs (ranibizumab; bevacizumab) that are effective for treating a disease of the eye, age-related macular degeneration. Both drugs bind to a growth factor, VEGF. Ranibizumab has been FDA-approved for macular degeneration (226). Bevacizumab has been FDA-approved for cancer treatment (227,228), but not for macular degeneration. According to Schmucker et al. (229), "[t]he costs of ranibizumab, however, are immense." The cost of bevacizumab is 40 times lower. Both drugs have similar efficacy against macular degeneration (230). Unfortunately, bevacizumab has increased safety risks. Schmucker concluded that if the, "higher rates of adverse effects [for bavacizumab] are subsequently confirmed to be higher in bevacizumab than in ranibizumab, some of the cost savings with bevacizumab may be negated" (231).

Yet another factor that enhances the prevalence of off-label use, and impairs utilization of the FDA-approval process where the result is an FDA-approved package label, is the following. This factor is expiration of the patent for the drug (232). In other words, if a patent that covers a specific drug has already expired, a pharmaceutical company would have little incentive to spend a million dollars on a

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