

## ON-LABEL AND OFF-LABEL USAGE OF PRESCRIPTION MEDICINES AND DEVICES, AND THE RELATIONSHIP TO CME

### BACKGROUND

Before a newly developed healthcare product can be marketed in the United States, the manufacturer must provide proof that the proposed product is safe and effective by satisfying rigorous research and clinical requirements of the Food and Drug Administration (FDA). Although the exact processes are a bit different, the goals of product development are the same for drugs, biologics and devices.

Once the product is approved, the manufacturer and the FDA agree on specific language describing indications, patient populations, dosage, route, conditions of usage, and other information to be included in the product's labeling (i.e., package insert, and where appropriate, manual). Using the product in compliance with the FDA required information is referred to as on-label use.

Off-label use of a prescription drug or device refers to the ability of licensed health care providers to prescribe or use the drug for indications, conditions, patients, dosages or routes of administration not yet evaluated and approved by the FDA. The decision to prescribe a prescription drug or use a device off-label should be based upon emerging science and clinical evidence and may or may not differ from the evidence used for the FDA to approve the product being on the market.

### MAGNITUDE OF OFF-LABEL USAGE

Reference to understanding the value and efficacy of off-label use of FDA approved medicines is contained in the 2009 Institute of Medicine report Initial National Priorities for Comparative Effectiveness Research.<sup>1</sup> Off-label use of medications is very common. Up to 20% of all drugs are prescribed off-label and among some classes of cardiac drugs, off-label use can be as high as 46%.<sup>2</sup> Many FDA approved drugs usually are not tested for safety and efficacy specifically in children. Therefore, it is believed that 50-75% of all medications prescribed by pediatricians in the U.S. are for off-label applications.<sup>3</sup>

With regard to medical devices, the patterns of off-label use are quite variable, with a range from single digits to up to 80% of use, depending on the novelty and availability of the device in the market. Devices are often introduced for a single use, with other uses identified by health care providers once the product is widely available. Companies often then evaluate the unapproved uses for on-label indications.

Some conditions can best be treated with off-label utilization of drugs or devices. An example is a congenital condition known as Kidney Reflux Disease, which mostly affects infants and young children. This disease is caused by improper development of the ureters which leads to a backflow of contaminated urine into the kidneys resulting in an infection. No medications have been approved to meet the needs for effective management of this condition. However, the off-label usage of multiple antibiotics has been shown to be the most effective course of treatment. Left untreated, Kidney Reflux Disease can lead to permanent damage and failure of the kidneys.<sup>4</sup>

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The two most common reasons for off-label usage of medicines and devices are:

1) To manage those diseases or indications for which a prescription medicine or device is currently being tested, has been tested or will be tested to assess the efficacy for a particular condition, and to include scientific evidence to suggest that the off-label usage of the product (prescription medicine) offers a viable alternative or clinical advantage over currently available options.

2) To prescribe doses of prescription drugs outside the range approved by the FDA. For example, this may be beneficial when an approved drug has been shown to improve the condition treated at higher doses than those used in clinical trials, or the condition has not shown improvement within the approved dosage range, or has produced unacceptable adverse effects in the prescribed dosage, but is well tolerated at a lower dose.

### **RELEVANCE OF OFF-LABEL USAGE TO CONTINUING MEDICAL EDUCATION (CME)**

Off-label discussion of product use is permitted within Certified CME activities when there is sufficient evidence for the off-label use and it is accepted within the medical profession as having adequate justification for the proposed use. Discussion must be at the discretion of the CME presenter without influence by the manufacturer or activity supporter.

Patients are served best when the provision of CME is based on the best available evidence. A presentation of an off-label indication within the context of a CME activity is intended to provide healthcare providers with the most current clinical evidence for all available treatment options and when other therapies are not available or have not benefited the patient. Such discussion must be evidence-based, should be strictly limited to the discretion of the accredited provider within the activity, and cannot be positioned to encourage or promote off-label use for commercial purposes. Sufficient evidence and a balance between a product's safety and efficacy must be presented to permit providers to make informed decisions when considering off-label drug use.

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1. <http://www.iom.edu/Object.File/Master/71/032/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web>
  2. David C. Radley, MPH; Stan N. Finkelstein, MD; Randall S. Stafford, MD, PhD. Off-label Prescribing Among Office-Based Physicians. *Arch Intern Med.* 2006;166:1021-1026.
  3. Roberts R, Rodriguez W, Murphy D, Crescenzi T: Pediatric drug labeling. *JAMA* 2003, 290:905-911.
  4. [http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/vesi\\_reflux.pdf](http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/vesi_reflux.pdf); <http://pediatrics.aappublications.org/cgi/content/full/118/2/698>