

## ***Position Statement***

# **Physician Directed Use of Medical Products**

*This Position Statement was developed as an educational tool based on the opinion of the authors. It is not a product of systematic review. Readers are encouraged to consider the information presented and reach their own conclusions.*

### **Definitions**

Off-label is a term describing the physician directed use of prescription drugs, biologics, and approved medical devices in a manner that is not specified in the labeling approved by the U.S. Food and Drug Administration (FDA). For cleared medical devices, off-label means any use that is not included in the cleared indications for use.” Labeling is considered any written material which accompanies, supplements, or explains the product.

### **Background - Practice of Medicine**

Currently, the practice of medicine presents difficult challenges for the orthopaedic surgical community to stay abreast of new and innovative medical developments that may advance patient care in an era when technological developments may rapidly outpace traditional educational opportunities for discussion and the regulatory review framework. It is not uncommon for some uses of medical products to become standard of care in the practice of medicine before there is approval or clearance of the labeled indications for use for a particular product.

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment.<sup>1</sup> The government has long recognized that physicians may prescribe or administer any legally marketed product for an off-label use within the practice of medicine. If physicians use a product for an indication not in the approved or cleared labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, to maintain awareness of the product's use and effects, and to discuss alternative treatments. The practice of medicine is regulated by state laws, and surgeons should adhere to all applicable state and federal laws and regulations.

### **FDA Regulatory Principles**

The FDA regulates the marketing approval or clearance, labeling, and promotion of pharmaceutical, medical device, and biologic products in the United States. These products may only be labeled, promoted, and advertised for the uses that the FDA has approved or cleared.

Promotion means all proactive activities (written, oral or otherwise) that directly or indirectly market, sell or support product sales and use, or that contribute to the sales growth of a company's products. For example, the FDA views promotion as including written labeling and advertising materials, interactions with sales representatives, company websites, dissemination of journal articles, and, in some cases, trade show presentations, physician training, and

reimbursement advice. Certain medical education activities also can stray into promotional conduct if undertaken for the purpose of inducing commercial sales.

FDA released updated guidance in 2014, intended to clarify their current thinking on the exchange of information related to unapproved new uses of drugs, biologics, devices, and combination products. FDA regulations do allow the exchange and dissemination of scientific information on a product's unapproved uses in certain circumstances. Types of scientific exchange include:

1. scientific or medical journal articles;
2. scientific or medical reference texts;
3. clinical practice guidelines.

## **Labeling**

The FDA and the manufacturer must negotiate the labeling claims of a medical product to ensure that the labeling accurately reflects the safety and effectiveness data presented in the manufacturer's marketing application. If surgeons are unsure of the labeled indication of the medical product, the FDA website<sup>3</sup> contains information for medical products on approved labeling and indications for use.

## **Restrictions on Distribution and Use**

In some circumstances, the FDA authorizes the use of risk, evaluation, and mitigation strategies (REMS) to limit the distribution of medical products to certain physicians or to restrict the distribution to particular patients. These products must be used according to their labeled indications. Another example of restricted distribution is humanitarian use devices that have been authorized for marketing for a rare disease or condition and which requires IRB approval for the use of the device for the FDA approved indication.

## **Special Populations**

In certain patient populations, off-label use of medical products is extensive where appropriate therapies are not available. Two of those populations include oncology and pediatric patients. Oncology patients depending on the type and severity of the disease are frequent recipients of off-label therapies. The FDA has recently recognized the need for accelerating the approval of cancer drugs. Pediatric surgeons are likely to use off-label therapies on neonates, infants, children, and adolescents due to the lack of medical products on the market labeled for use in these populations. Surgeons find a lack of approved pediatric devices for many reasons including a historical exclusion of children in medical trials, and liability concerns among other issues. In 2007, the Congress recognized significant issues with pediatric device development and signed the Pediatric Medical Device Safety Act into law as part of the Food and Drug Administration Act Amendments of 2007.

## **Best Practices and Professional Standards**

There are instances when the off-label use of medical products has evolved to be recognized as a generally accepted medical standard within the physician community. Public health agencies, such as CMS, have authorized reimbursement of off-label use of approved products in specially defined circumstances where such use is recognized under generally accepted medical standards. Standard of care changes over time and new literature may continually alter the legal landscape. Surgeons should adhere to best medical practices in the off-label use of legally marketed products. Surgeons should appropriately counsel patients about the benefits and risks of the proposed treatment, and alternative treatments that might be available. Surgeons are

encouraged to report adverse events occurring with the off-label usage of medical products to manufacturers and/or appropriate federal authorities.

Orthopaedic surgeons should be aware of company sales and marketing tactics that may undermine the free and credible exchange of scientific information on new products and technologies, including inappropriate product comparisons between FDA approved and cleared products, misleading claims regarding product safety, efficacy and outcomes, the dissemination of biased clinical data, and the omission of adverse clinical data.

Orthopaedic surgeons should be aware of the potential that certain interactions may create an actual or potential conflict of interest in advancing new scientific and clinical information to the orthopaedic surgeon community and avoid compromising situations that may call independent medical judgment into question. The orthopaedic surgical community should rely for guidance on the *AAOS Standards of Professionalism on Orthopaedic Surgeon-Industry Relationships* in evaluating industry interactions that directly or indirectly involve communications relating to the use or recommended use of unapproved products.

Orthopaedic surgeons with compensated arrangements with industry should undertake appropriate precautions and financial disclosures in CME, grand rounds and other medical education and professional activities that may involve communications and interactions regarding the off-label use of products and avoid scenarios in which the surgeon is used in white coat marketing activities that are promotional in nature.

### **Enforcement Actions and Trends**

Physicians and surgeons are not insulated from the law if they are engaging in sales and marketing activities on behalf of or in conjunction with manufacturers. The off-label promotion of medical devices is expected to have increased scrutiny from federal authorities. Violations of the federal False Claims Act are cited in *qui tam* suits which may or may not also allege conflicts of interest with certain manufacturers.

***The American Academy of Orthopaedic Surgeons (AAOS) believes that surgeons may prescribe or administer any legally marketed product for an off-label use within the authorized practice of medicine in the exercise of appropriate medical judgment for the best interest of the patient. If surgeons use a product for an indication not in the approved or cleared labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain awareness of the product's use and effects. Surgeons should appropriately counsel patients about the benefits and risks of the proposed treatment, and alternative treatments that might be available. In the case of an adverse event with an off-label use, surgeons can submit a report to the manufacturer and/or the FDA. Orthopaedic surgeons should disclose all conflicts of interest to patients, institutions, and medical associations and adhere to all state and federal laws and regulations.***

**References:**

1. U.S. Food and Drug Administration, Guidance for Institutional Review Boards and Clinical Investigators: "Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices. 1998 Update.  
<http://www.fda.gov/oc/ohrt/irbs/offlabel.html>
2. U.S. Food and Drug Administration, Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses-Recommended Practices. February 2014.  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm400104>
3. <http://www.fda.gov>

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## Frequently Asked Questions About Physician Directed Use

### **Q. What is off-label use?**

**A.** "Off-label" or physician directed use for prescription drugs, biologics, and approved medical devices means any use that is not specified in the labeling approved by the U.S. Food and Drug Administration (FDA). For cleared medical devices, "off-label" means any use that is not included in the cleared "indications for use." Labeling is considered any written material which accompanies, supplements, or explains the use, purpose, and indications of the product.

### **Q. The term "off-label use" seems pejorative. What other terms are used to describe off-label use?**

**A.** The phrase "physician-directed application" is used by some physicians and surgeons.

### **Q. Where do I find out the specific labeled indications for use on a product that I'm using?**

**A.** Labeling information is available on material accompanying the medical product. For the most current device labeling information, orthopaedic surgeons should contact the product manufacturer's representative. The FDA website will not contain the most up-to-date labeling information for Class III or pre-market approval (PMA) devices, due to frequent supplemental approval applications. The FDA's 510k data base does not contain labeling information on 510k cleared devices.

### **Q. Does the FDA regulate the practice of medicine?**

**A.** No. The FDA by law does not regulate or assert legal jurisdiction over the practice of medicine. State law provides the authority and legal standards for the practice of medicine.

### **Q. How does FDA regulate manufacturers in connection with the promotion of company products?**

**A.** The FDA regulates manufacturers in the advertising and promotion of approved and cleared company products. FDA regulations prohibit the advertising and promotion of the off-label use of medical products. An off-label use of a medical product cannot be described by the company as safe and effective for a particular use.

### **Q. Are surgeons entitled to receive scientific information relating to unapproved products and technologies?**

**A.** Yes. Companies may provide unbiased, non-misleading scientific and clinical information regarding their products in response to an unsolicited request for information from a surgeon.

### **Q. Can company representatives provide technical support in the operating or procedure room when the procedure or product involves an off-label use?**

**A.** No, company representatives are not allowed to provide technical or verbal guidance for an off-label use.

### **Q. How is standard of care determined?**

**A.** Standard of care changes over time due to the available literature, use of medical products, and outcomes of medical and product liability legal cases. It is not uncommon for some technologies to become standard of care in the practice of medicine before there is formal regulatory approval or clearance of a particular product.

**Q. In practical terms, what happens when a manufacturer attempts to run a clinical trial on a marketed product in order to claim another indication on their labeling?**

A. Identifying and enrolling patients in such trials is often difficult since the product is available on the market and is often used in an off-label manner. Patients are increasingly unwilling to be randomized in these trials when they can acquire the marketed product for the off-labeled indication from a physician or surgeon.

**Q. Since the FDA does not regulate the practice of medicine, can I use a product in any manner in which I choose?**

A. A physician may use a medical product for an indication not in the approved or cleared labeling. Physicians and surgeons should be well informed about the product and base the use on firm scientific rationale and sound medical evidence. Surgeons should counsel patients about the benefits and risks of the proposed treatment and alternative therapies that may be appropriate.

**Q. Is the consent process sufficient for the off-label use of a medical product?**

A. Institutions/facilities have different practices for issuing informed consent and the documentation of off-label use. Additionally, some physicians may not be aware of the labeled indication of the medical product and may unknowingly use a product in an off-label manner. Surgeons may want to explain to patients that within the practice of medicine, physicians may choose a treatment option that is off-label if it is in the best interest of the patient. Surgeons may want to document the planned use of off-label products in the medical chart.

**Q. Should I document the use of off-label medical products in the patient's medical chart?**

A. Documentation in medical charts may vary according to the standard of care of the product and the availability of "on-label" products to treat the medical condition.

**Q. What should I do if I find that a patient has experienced an adverse event with the off-label use of a medical product?**

A. Physician reporting of adverse events is voluntary. Adverse events can be reported to the FDA's Medwatch system at:

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm>

Physicians and surgeons may want to alert the hospital and contact the company to ensure that it is aware of the problem.

User-facilities, such as hospitals and nursing homes, are legally required to report suspected medical device-related deaths to both FDA and the manufacturer, if known, and to report medical device-related serious injuries to the manufacturer or to FDA, if the manufacturer is unknown.

**Q. What are the latest enforcement trends regarding off-label use?**

A. Recently, there have been several significant government enforcement actions against pharmaceutical and other companies for off-label advertising and promotion of FDA approved or cleared products to physician communities. These enforcement actions reveal industry tactics that may manipulate, distort and undermine the natural and essential collaboration and exchange of scientific and medical information between academia, physicians and industry.

Physicians and surgeons are not insulated from the law if they are engaging in sales and marketing activities on behalf of or in conjunction with manufacturers. The off-label promotion of medical devices is expected to have increased scrutiny from federal authorities. Violations of the federal False Claims Act are cited in *qui tam* suits which may or may not also allege conflicts of interest with certain manufacturers.

**Q. What do conflicts-of-interest have to do with off-label use?**

**A.** Federal government agencies and Members of Congress have increased their scrutiny of conflicts-of-interest in response to the filing of *qui tam* suits. These suits allege that employees or consultants of medical device, biologic, or device manufacturers engage in illegal marketing schemes to promote the use of a medical product for unapproved, cleared, or licensed indications.

In July 2007, Jazz Pharmaceuticals agreed to pay the government \$20 million to settle criminal and civil allegations in an off-label marketing investigation. A psychiatrist was charged with violating criminal misbranding provisions of the Food, Drug and Cosmetic Act after he gave talks around the country promoting a drug for off-label uses. The psychiatrist was a consultant of Jazz Pharmaceuticals and also advised physicians how to conceal off-label uses from insurers to maximize reimbursements.