



Sound Policy. Quality Care.

December 21, 2023

Lauren K. Roth
Associate Commissioner for Policy
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted electronically via regulations.gov

Re: Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers

Dear Associate Commissioner Roth:

The Alliance of Specialty Medicine (the “Alliance”) represents more than 100,000 specialty physicians from 16 specialty and subspecialty societies who are dedicated to the development of sound federal health care policy that fosters patient access to the highest quality specialty care. We appreciate the opportunity to provide feedback regarding the aforementioned second revised draft guidance from the perspective of specialty physicians.

Physician-directed applications of approved or cleared medical products (i.e., “off-label” uses) are integral to specialty medicine. For the conditions specialists diagnose, manage, and treat, physician-directed applications may be widely recognized as the standard of care and recommended in practice guidelines. As explained in our position statement,

To enhance patient care, physicians must have unrestricted access to truthful, non-misleading information about the benefits and risks of all therapies available for treatment, including medically accepted alternative uses of approved prescription drugs, biologics, and/or devices. Manufacturers must be able to provide adequate directions for use of both approved and medically accepted alternative indications of approved medicines and treatments, along with adequate disclosures regarding risks and the limitations of scientific understanding.

We commend FDA for making a concerted effort “to strike a careful balance between supporting [health care providers’] interest in scientific information about unapproved uses of approved/cleared medical products to inform clinical practice decisions for the care of an individual patient, and mitigating the potential that the government interests advanced by these statutory requirements will be undermined,” in this second revised draft guidance.

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American Academy of Facial Plastic and Reconstructive Surgery • American Academy of Otolaryngology-Head and Neck Surgery
American Association of Neurological Surgeons • American College of Mohs Surgery • American College of Osteopathic Surgeons
American Gastroenterological Association • American Society for Dermatologic Surgery Association
American Society of Cataract & Refractive Surgery • American Society of Echocardiography • American Society of Plastic Surgeons
American Society of Retina Specialists • American Urological Association • Coalition of State Rheumatology Organizations
Congress of Neurological Surgeons • National Association of Spine Specialists • Society of Interventional Radiology

The Alliance agrees with the FDA that “[scientific information about unapproved use] communications be truthful, non-misleading, factual, and unbiased.” We support firms providing “all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information” in those communications, and if it is clinically relevant, providers may apply the information in clinical practice and for individual patients.

We urge the FDA to ensure that access to scientific information from manufacturers on the safe and effective approved and unapproved use of medical products is not disrupted when the guidance is finalized.

The Alliance appreciates the opportunity to share feedback on this guidance and the impact on specialty medicine and patients. Should you have any questions, please contact us at info@specialtydocs.org.

Sincerely,

American Academy of Facial Plastic and Reconstructive Surgery
American Academy of Otolaryngology-Head and Neck Surgery
American Association of Neurological Surgeons
American College of Osteopathic Surgeons
American Gastroenterological Association
American Society for Dermatologic Surgery Association
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National Association of Spine Specialists
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Physician-Directed Applications

A Position Statement of the Alliance of Specialty Medicine

Physician-Directed Applications

Physician-directed applications, also known as “off-label”¹ uses, are an integral component of the art and science of medical practice, particularly for specialty physicians. Using their medical expertise and judgment, physicians may choose to use approved medical products such as prescription drugs, biologics, and devices, for uses not listed in the United States Food and Drug Administration (FDA) approved or cleared labeling, as appropriate.

Background

It is not uncommon for some off-label uses of medical products to become standard of care in the practice of medicine.² In fact, off-label uses of certain medical devices and drugs can be found in standard textbooks for medical subspecialties. In certain patient populations, such as children and cancer patients, off-label use of medical products is extensive when appropriate therapies have not been developed or evaluated for the populations or a clinical trial is not feasible (such as in the case of rare diseases). In these circumstances, physician-directed applications provide treatments that may not otherwise be available for some of the nation’s youngest and most critically ill patients.

Physicians use the best available clinical evidence, judgment, and consideration of individual patient circumstances and preferences in treating and managing disease and injury. Good medical practice and the best interests of the patient require that physicians use legally-available drugs, biologics, and devices according to their best clinical expertise and judgment.

FDA Regulatory Principles and Labeling

The FDA has broad regulatory authority over the approval of pharmaceutical, medical device, and biologic products in the United States. Products may only be labeled,

¹ “Off-label” use for approved prescription drugs, biologics, and medical devices means any use that is not specified in the labeling approved by the FDA. For cleared medical devices, “off-label” means any use that is not included in the cleared “indications for use.” Labeling is considered as any written material, which accompanies, supplements, or explains the product.

² Refer to specific specialty examples document at specialtydocs.org

promoted, and advertised for the uses that the FDA has approved or cleared. Labeling of a medical product is negotiated between the FDA and the manufacturer to ensure that the labeling accurately reflects the safety and effectiveness data presented in the manufacturer's marketing application. Furthermore, a drug, device, or biologics manufacturer may choose, for economic reasons, not to pursue additional labeling for indications that may increase the cost of obtaining FDA approval or clearance. As a result, the label may not reflect changes in indications, contraindications, warnings, or dosage, supported by new data that become available after approval or clearance.

Practice of Medicine Exception

The Food and Drug Administration does not have the statutory authority to regulate the practice of medicine. In 1998, the US Supreme Court issued a judgment in *Buckman v. Henney* affirming physicians' right to use any FDA-approved therapies they believe are in the best interests of their patients. In addition, section 906 of the federal Food, Drug, and Cosmetic Act addresses the issue of the practice of medicine and states the following:

Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.

Physicians may prescribe or administer any legally-marketed product for an off-label use within the practice of medicine.

Standards of Care

Standards of care change over time, and the emergence of new literature may alter treatment patterns. As a result, there are instances when the off-label use of medical products evolves to be recognized as a generally accepted medical standard. There are also instances in which the labeled uses of medical products are found to have contraindications and interactions that reduce their safety and efficacy. Specialty physicians are encouraged to notify the relevant agency or institution of adverse events related to the use of medical products.

Access to Available Information

To enhance patient care, physicians must have unrestricted access to truthful, non-misleading information about the benefits and risks of all therapies available for treatment, including medically accepted alternative uses of approved prescription drugs, biologics, and/or devices. Manufacturers must be able to provide adequate directions for use of both approved and medically accepted alternative indications of approved medicines and treatments, along with adequate disclosures regarding risks and the limitations of scientific understanding.

Provided there is prominent disclosure that FDA does not approve such use, limitations on communications should only be related to patient risk based on factors including the approval status of the medicine, general medical acceptance of the treatment, and the level of scientific sophistication of the audience.

Informed Consent

Informed consent is the process by which the treating health care provider discloses appropriate information to a competent patient so that the patient may make a voluntary choice to accept or refuse treatment.³ Among other things, informed consent requires a discussion of reasonable alternatives to the proposed intervention, which may include a discussion of medically accepted alternative uses of approved prescription drugs, biologics, or devices.

Physicians and medical institutions have varied practices for obtaining and documenting informed consent provided to patients that may or may not address off-label use. In some instances where an off-label use has come to be considered a standard of care in the clinical community and/or raises little risk of an adverse outcome, the use may not be discussed specifically with the patient. However, physicians should use their clinical judgment in determining the need to discuss specific off-label uses with patients and include information about such uses in informed consent materials when the off-label use could be a significant factor in the patient's decision about whether to undergo the procedure. If a patient has questions, the physician should also personally inform the patient that the product is being used in an off-label manner and discuss the benefit/risk profile for that use. This approach not only serves the patient's best interests, but might also help to limit the physician's liability risk.

Benefits and Risks of Physician-Directed Applications

Benefits and risks exist with off-label use. Benefits include the ability to provide care to patients who may not receive appropriate treatment or perhaps treatment at all without off-label use, such as many pediatric patients. Risks include the potential for

³ Appelbaum PS. Assessment of patient's competence to consent to treatment. *New England Journal of Medicine*. 2007; 357: 1834-1840.

limited effectiveness and unexpected side-effects from uses that have not been adequately studied for the specific indication or patient population.

It is well-established that physicians who use a product for an indication not in the approved or cleared labeling have the responsibility: (1) to be well informed about the product; (2) to base its use on a firm scientific rationale and sound medical evidence; and (3) to maintain awareness of the product's uses and effects.

Conflicts of Interest

Conflicts of interest should be disclosed in compliance with all state and federal laws and regulations. Specialty physicians engaging in compensated arrangements with industry should disclose their financial arrangements in medical education, research, and professional activities. Physicians who are involved in product development and/or testing should disclose this role to patients. Physicians should avoid interactions and activities where discussions of off-label use could be considered promotional in nature.

Statement of Policy

The Alliance of Specialty Medicine maintains that a specialty physician may prescribe or administer any legally-marketed product for an off-label use within the authorized practice of medicine where the physician exercises appropriate medical judgment and it is in the best interests of the patient. If specialty physicians use a product for an indication not in the approved or cleared labeling, they have the responsibility: (1) to be well informed about the product; (2) to base its use on a firm scientific rationale and sound medical evidence; and (3) to maintain awareness of the product's use and effects. Specialty physicians should appropriately counsel patients about the benefits and risks of the proposed treatment, and whether alternative treatments might be available. Specialty physicians are encouraged to notify the relevant agency or institution of adverse events related to the use of medical products.