Healthcare
INBRIEF®

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Off-label Product Use: Basic Risk Management Considerations

FDA-approved medications and medical devices are required to have a label that lists clinical indications for product use. When providers prescribe approved drugs or employ approved devices for purposes not listed on the label, these uses are considered "off-label."

After consulting evidence-based medical literature, physicians occasionally may determine that a drug or device could be beneficial for conditions other than those approved or cleared by the FDA. Examples of off-label use include the following, among others:

- **Botulinum toxin,** approved for muscle dystonia and limb spasticity, to treat depression.
- **Tricyclic antidepressants,** approved for depression, to treat neuropathic pain.
- **Arterial dilatation balloons,** approved for use in adults, to be used in children.

Other common instances of off-label use include altering standard dosages, modifying the length of time medications are given and prescribing drugs to untested age groups.

Although a common and often advantageous practice, off-label use can present certain risks to both patients and providers. (See "Top Five Adverse Outcomes Associated with Off-label Drug Use" at right.) Negative patient outcomes may result in claims against organizations and/or providers alleging negligence and failure to obtain informed consent. In addition, imprudent off-label prescribing may have regulatory consequences, such as penalties and enforcement actions.

Top Five Adverse Outcomes Associated with Off-label Drug Use

1. Nonspecific gastrointestinal symptoms
2. Hemorrhage
3. Anticholinergic syndrome
4. Neuroleptic malignant syndrome
5. Accidents and injuries due to drug side effects, interactions or misuse

Source: Han, N. et al. "Adverse Events Related to Off-label Drugs Using Spontaneous Adverse Event Reporting Systems." *Therapeutics and Clinical Risk Management.* August 21, 2021, volume 17, pages 877-887.

This edition of *inBrief*® suggests a range of risk management considerations and strategies relating to off-label use of FDA-approved products. Also included is a clinical action plan intended to help healthcare facilities and practices enhance implementation and documentation of critical organizational processes – such as policy-making, patient selection, informed consent and adverse event reporting – associated with unapproved uses of approved drugs and medical devices.

Risk Management Considerations

Be aware of the legal and regulatory environment. The FDA views off-label use as a proper extension of the practice of medicine. The agency notes that prescribing providers should be familiar with the product, base the decision on scientific rationale and established guidance, and maintain records of the product's use and effects.

Most states do not have explicit prohibitions on off-label prescribing by nurse practitioners (NPs) and physician assistants (PAs). In general, unless the practice agreement with the supervising physician has express restrictions on off-label use, NPs and PAs may prescribe medical products for a non-FDA approved purpose if the use is supported by peer-reviewed literature. (For additional information, see Baldrige, K. "Off-Label Prescribing: Implications for Nurse Practitioners," posted on *Advanced Practice Education Associates.com*, and "Off-label Considerations for Mid-level Practitioners," posted on *AmericanMedSpa.org*, January 18, 2019.)

Although not prohibited, off-label use has its limits, as the federal government has issued enforcement actions against manufacturers for directly promoting unapproved uses in order to boost sales.* Off-label applications most susceptible to critical review include drug doses that exceed approved amounts, as well as using drugs to treat non-listed patient populations or indications.

To maintain compliance, providers and facilities must be cognizant of enforcement actions, regulatory developments and industry guidance statements. The FDA offers regular updates regarding product status on a subscription basis and hosts these searchable databases, among others:

- Approved drugs database
- Biologics products and establishments
- Device approvals, denials and clearances
- Medical device databases
- MedWatch safety information and adverse event reporting program

Ascertain the standard of care. Providers have a duty to maintain a working knowledge of both the medications they prescribe and the medical devices they utilize, and to remain current on the applicable standard of care. They should ensure that off-label uses are supported by reputable peer-reviewed literature and reflect the recommendations of national drug compendia, professional association guidelines and industry consensus statements, where available.

The following agencies and organizations, among others, offer information relating to off-label use and practices:

- Agency for Healthcare Research and Quality
- American Academy of Orthopaedic Surgeons
- American Academy of Pediatrics
- American Psychiatric Association
- Centers for Medicare & Medicaid Services
- Clinical Pharmacology
- FDA, Daily Med; Medication Guides; and Products and Medical Procedures
- National Comprehensive Cancer Network Drug and Biologics Compendium
- United States Pharmacopeia

Heed label warnings. "Black box" warnings – so called for the black borders that signal the strongest label warnings issued by the FDA – alert healthcare professionals and consumers to potentially serious and even life-threatening consequences if the product is used outside of FDA-approved indications. Black box warnings typically signal that a drug or device has been approved for restricted use only, and any application beyond these boundaries may violate the standard of care. Whenever a black box warning is overridden, the provider should note the medical rationale in the patient healthcare information record. In addition, clinical safety measures taken – such as additional patient monitoring and supervised administration or use of the product in question – should be documented. (For additional information, see Axelsen, F. "Black Box Warnings – Legal Risks That Many Physicians Never See Coming." *Medscape*, October 27, 2021. Available by subscription.)

Know the risks of improvised medical device use. When supplies run short, it may be tempting to expand medical device indications beyond FDA parameters or to modify a device to suit immediate needs. However, improvised use of medical devices can result in serious patient injury, with regulatory and/or liability consequences. In addition to performing regular inspections and preventive maintenance on all medical devices, facilities should educate providers about the following issues, among others:

- **Risks associated with device improvisation,** including equipment limitations and potential for user error.
- **Documentation requirements,** reinforcing the message with regular reminders.
- **Adverse event reporting requirements,** both internal and external.
- **The need to notify professional liability insurers** of any device manipulation or modification.

Understand how *off-label, investigative, compassionate* and *emergency* uses differ. In general, if a provider intends to use an FDA-approved product off-label in furtherance of the practice of medicine, it does *not* require submission to the FDA of an Investigational New Drug Application or Investigational Device Exemption. Submission is required *only* if the use is for the purpose of clinical investigation or research and is guided by a clinical study protocol.

To avoid potential confusion between standard off-label and investigative use, the provider should first verify that the proposed drug or device application is not under investigation by the FDA. In addition, the patient healthcare information record should reflect that the product is being utilized in the best interest of the individual patient to treat an existing condition. (For more information, see the FDA guidance "'Off-Label' and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices.")

* The Federal Food, Drug, and Cosmetic Act addresses the issue of misbranding prescription drugs or medical devices due to false or misleading labeling. (See 21. U.S.C. §§ 331(a) and 352(a)).

When an investigational medical product is used outside of a clinical trial when no other viable therapeutic options exist, the practice is referred to as *compassionate* or *expanded use*. Compassionate use requires prior review and approval, even if only one patient is being treated.

Emergency use refers to the utilization of an investigational product that has *not* been approved by the FDA in a life-threatening or medically debilitating medical situation, or during a declared state of emergency, such as a pandemic. For details and reporting requirements, see the FDA information sheet "Emergency Use of an Investigational Drug or Biologic."

Off-label use of FDA-approved medications and devices is an ethically and legally accepted practice. However, the attendant risks must be understood and carefully managed. By complying with relevant regulations, professional guidelines, product warnings, and documentation and reporting requirements, providers and organizations can meet their patients' wide-ranging treatment needs in a safer manner, while minimizing liability exposure.

Clinical Action Plan: Enhancing Off-label Use and Related Documentation

Focus Area	Initiatives	Action Status
Review and approval of off-label use	**For facility leadership:**	
	1. **Draft a facility policy addressing off-label use**, including documentation requirements.	
	2. **Verify professional liability insurance coverage** before authorizing off-label use.	
	3. **Query providers regarding any financial arrangements with the manufacturer** before approving off-label use of a medical product.	
	For healthcare providers:	
	1. **Notify facility leadership** prior to using a drug or medical device in an off-label manner.	
	2. **Verify that "on-label" treatments have been considered** prior to off-label use.	
	3. **Note how long the drug or device in question has been approved** and in general use.	
	4. **Determine whether the proposed off-label use is considered accepted practice** by reputable providers and organizations.	
	5. **Rely on valid medical and scientific data,** ideally from product manufacturers that adhere to the FDA's recommended "Good Reprint Practices."	
	6. **Facilitate tracking of off-label use outcomes** by documenting patient and provider name, product serial and lot number, and dates of usage.	
Patient selection and rationale	1. **Ensure that providers first consider the risks of any proposed off-label use,** including:	
	• **Known contraindications,** side effects and adverse drug interactions.	
	• **Patient medical conditions or past treatments** that might preclude or affect use.	
	• **Patient risk factors** – such as health status, medication use and age.	
	2. **Instruct providers to note the following in the patient healthcare information record**:	
	• **FDA-approved use of the drug or device** and the intended off-label use.	
	• **Results of earlier treatment attempts** and diagnostic findings that support off-label use.	
	• **Supporting rationale** for the proposed off-label use, citing scientific and medical evidence.	
	3. **Educate providers on the need to monitor patients** during and after off-label treatment, and to document any side effects or adverse reactions.	

Focus Area	Initiatives	Action Status
Informed consent and disclosure of risks	1. **Develop educational tools** to inform patients about proposed off-label uses, including the purpose(s) for which the drugs or devices have been approved by the FDA.	
	2. **Discuss risks, benefits and "on-label" alternatives with patients,** and document the discussion in the patient healthcare information record.	
	3. **Document any inquiries from the patient,** as well as responses.	
	4. **Require patients to sign a standardized informed consent form** for off-label use, including:	
	• **Details of the treatment,** rendered in easily understood terms.	
	• **A list of known risks and potential complications** associated with the off-label application, including a disclaimer that all associated risks may not be known.	
	• **A warning statement** noting that a successful outcome cannot be guaranteed and the patient is under no obligation to proceed.	
Adverse event reporting	1. **Adopt a facility policy regarding documentation and reporting of observed problems** to internal patient safety programs, manufacturers and appropriate authorities.	
	2. **Compile and evaluate reports of adverse patient occurrences** associated with off-label use via established quality improvement channels.	
	3. **Report adverse events and patient injuries to the FDA** via the MedWatch voluntary reporting program, as well as to designated safety organizations and oversight entities.	
	4. **Notify patients in a timely manner if product recalls affect on- or off-label use** and document such in the patient healthcare information record.	

Quick Links

- Furey, K. and Wilkins, K. "Prescribing 'Off-Label': What Should a Physician Disclose?" *American Medical Association Journal of Ethics*, June 2016.
- "Off-Label Use of Prescription Drugs," issued by the Congressional Research Service, February 23, 2021.
- Syed, S.A. et al. "The Law and Practice of Off-Label Prescribing and Physician Promotion." *The Journal of the American Academy of Psychiatry and the Law*, posted November 2020.

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