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Non-FDA-Approved Use of Medical Products:
Pitfalls to Avoid

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By Kelly Riedl, PA-C, CPHRM

Non-FDA-Approved Use of Medical Products:
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INTRODUCTION

Medical products including drugs, devices, and biologics are regulated by the U.S. Food and Drug Administration (FDA). The basic steps leading to the development and ultimate approval of medical products are similar, but the process details vary within each step for drugs versus devices.[1] These basic steps include:[1]

1. **Discovery/Concept** with research beginning in the lab.
2. **Preclinical Research** in the lab and on animals to ensure basic safety.
3. **Clinical Research** on people through clinical trials to further gauge safety and effectiveness.
4. **FDA Review** of submitted data by teams to make approval decision.
5. **FDA Post-Market Safety Monitoring** after approval to ensure continued safety.

During the clinical research step, medical products are considered investigational and thus not generally available for patients who are not involved in associated clinical trials. An exception to this rule called "compassionate use" expands access to investigational medical products outside of clinical trials for patients with serious or immediately life-threatening medical conditions.[2] By definition, these patients are at a stage of disease where there is a reasonable likelihood that death will occur within months without treatment.[3]

If during the FDA review step the medical product is shown to be safe and effective for its intended use, meaning the benefits prove to outweigh the risks, the medical product will be approved for market. Part of the approval process includes labeling, which is proposed by the manufacturer and reviewed by the FDA. Upon approval, the medical product is labeled with the necessary information for clinicians and patients to ensure safe use. An exception to this process is "emergency use authorization," which gained familiarity during the COVID-19 pandemic. When the U.S. Department of Health and Human Services declares emergency use authorization is appropriate to ensure medical countermeasures are available during a public health emergency, this allows the FDA to authorize unapproved medical products or unapproved uses of approved medical products.[4]

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OFF-LABEL USE OF MEDICAL PRODUCTS

When a medical product is used in a way that is not consistent with the FDA-approved labeling, this is considered off-label use. With regard to drugs, the FDA describes this as using the drug for a medical condition it has not been approved to treat, using the drug in a different way, or using the drug in a different dose than approved.[5] Off-label drug prescribing is common, with an average of one in five prescriptions written for off-label use.[6] Patient populations that are more likely to be prescribed medications off-label include children, pregnant women, and people with psychiatric disorders since they are less often eligible for clinical trials.[7]

Compounded drug formulations are common examples of off-label drugs. These can be used for patients who need a medication but are unable to use it in the FDA-approved form. Reasons for this include allergies to certain inactive ingredients such as dyes, or inability to swallow pill formulations resulting in the need to create a liquid form.[8] Another reason for use of compounded drug formulations is during times of drug shortages. While compounding pharmacies are not typically allowed to make copies of approved drugs, there is an exception under the Federal Food, Drug, and Cosmetic Act if the drug is listed on the FDA drug shortages list.[9] While compounded drugs play an important role for many patients, they are not FDA-approved and do not undergo testing for safety and quality. This adds additional risk for patients and potentially for prescribers.

The Risk Management department assists insureds with a variety of liability concerns and questions daily through the Risk Management Helpline. Questions regarding off-label use of medical products is a frequent question from insured physicians and underwriters accounting for up to 44% of inquiries handled each month over the past year. Most recently, this has been driven by the surge in off-label prescribing, compounding, and dispensing of weight loss medications. Other questions center around use of intravenous vitamins and minerals, protein-rich fibrin injections, and amniotic fluid products. In most instances, the physician or underwriter wants to better understand the risks of using medical products off-label, if this is or should be a covered activity under their policy, and how to lessen liability exposure in the event they adopt offering these treatments. This article intends to offer risk reduction strategies on these common questions related to the use of non-FDA-approved medical products by exploring lessons learned from closed claims.

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CASE ONE:
Ineffective Informed Consent

Informed consent to medical treatment is fundamental in both ethics and law. It empowers patients to make well-considered decisions about their treatment after understanding the risks, benefits, and alternatives. When patients encounter a complication that they did not understand to be an associated risk of treatment, this can increase the likelihood of a negligence claim. In these situations, generally the claimant will allege that the physician failed to disclose information that the patient should have had to make an informed decision about the treatment. The following case examines how an ineffective informed consent process negatively impacted the defensibility of a claim.

As you review this case consider your process for properly vetting new treatment offerings in your practice to ensure safety and efficacy.

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A 50-year-old female presented to an aesthetic medicine clinic for treatment of three right lower extremity lipomas. She had received a variety of treatments with this clinic's physician over the years for other aesthetic concerns including sclerotherapy and facial injections.

After assessing the lipomas, the physician recommended lipolysis to dissolve the fatty tumors. She explained the treatment being offered was new and the medication being utilized for the treatment was "off-label." The patient consented to this procedure and approximately 50 cc of the fat-dissolving solution was injected into each lipoma.

Four weeks later the patient returned for follow-up and reported the treated areas were swollen, painful, and the skin was darkening. The physician assessment was inflammation and necrosis of the treated lipomas, and the patient was instructed to apply warm moist heat to the areas throughout the day, apply antibiotic ointment, and keep covered with bandages. She was instructed to return the following week for a follow-up appointment.

The following week the patient returned and reported some improvement in the pain. The physician's assessment indicated the areas were firm to the touch but minor improvements in overall appearance were noted. She was instructed to follow up again in one week.

After two more weeks of follow-up with similar progress the patient was referred to a wound care specialist for possible debridement. Instead she followed up with her plastic surgeon. The plastic surgeon assessed the patient and diagnosed her with full thickness tissue necrosis. He recommended wound debridement and placement of a wound vacuum-assisted closure (VAC) dressing system to assist with healing. She proceeded with this treatment plan and underwent wound debridement surgery.

Over the next two months following this surgery, the patient continued to use the wound VAC and saw a wound care nurse three times a week. After the wound VAC was removed, the patient continued to follow up with her plastic surgeon to monitor the continued slow healing. Her wounds eventually healed approximately a year after her initial debridement, but she was left with significant scarring and lost her job due to the lengthy healing process. She planned to undergo additional surgery to address the scars when financially feasible.

The patient pursued a claim against the aesthetic medicine physician for the damages that resulted from the fat-dissolving injections.

DISCUSSION

Expert reviewers were unsupportive of the care provided by the aesthetic medicine physician with criticisms mainly centered on the informed consent process. The informed consent documentation reflected that the fat dissolving solution was being used off-label; however, this medication was not FDA approved for any use, thus was being used without label. Additionally, the possibility of the patient's complication or similar complication was not outlined as a risk of the procedure in the informed consent.

This case was further complicated by the plastic surgeon's documentation, which stated the patient was talked into having the lipolysis treatment when the aesthetic medicine physician noticed her lipomas during her sclerotherapy treatment. Additionally the FDA released cautionary statements warning that this fat-dissolving medication was not FDA approved for any use and had caused serious adverse events. These factors would pose significant difficulties for the defense to argue that the plastic surgeon met the standard of care in recommending this treatment. Additionally there were concerns that the plaintiff's attorney could easily poke holes in multiple aspects of her informed consent process proving it ineffective. For these reasons the case was ultimately settled with a payment to the patient.

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RISK REDUCTION STRATEGIES

Effective and thorough informed consent practices may deter non-meritorious claims that are based on unrealistic expectations or misunderstandings. Thorough documentation throughout this process becomes a physician's best defense because it is stronger evidence than patient testimony. Consider the following strategies to optimize your informed consent process:

- Prior to offering new treatments, ensure that you have done ample research, understand the FDA labeling status, and market the product truthfully.
- Remember that informed consent is a process, not just a signed form, that involves three vital steps including **discussion**, **decision**, and **documentation**.
- Conduct the **discussion** in easily understood lay terminology and include the following elements:
  - Diagnosis
  - Recommended treatment
  - Alternative treatments
  - Prognosis/risks/benefits including what may happen if no treatment occurs
- During the **decision**, assess the patient's ability to understand relevant medical information, implications of treatment, and alternatives.
- **Document** the informed consent process in the patient's medical record, including:
  - An informed consent discussion occurred, which included the associated risks, benefits, and alternatives.
  - The patient had the opportunity to ask questions.
  - The patient understood the information provided, the possible risks, and agreed to proceed with or refuses treatment.
  - A brief description of any handouts or supplemental educational material provided.
- Obtain the patient's signature on a consent form to provide evidence that an informed consent discussion occurred.
  - Consider using procedure-specific forms that identify the most common risks and complications. Provide space to list additional risks and alternatives, depending on the patient's condition.
  - Include the physician and patient signatures, date, and time.
  - In some jurisdictions, state law dictates provisions that must be included in informed consent forms. Be sure to comply with your state's requirements.

ADDITIONAL RESOURCES

The Joint Commission: *Informed Consent: More than Getting a Signature*[10]
Actionable strategies for healthcare organizations to improve the process of informed consent and enhance patient safety

American Medical Association (AMA): *7 Complex Words You Shouldn't Include on Your Consent Form*[11]
Strategies for improving consent readability to ensure an effective and ethical informed consent process

ProAssurance Risk Management Guidelines: *Informed Consent*[12]
Additional key considerations and risk reduction strategies to further support your practice's informed consent process

ProAssurance: *Sample Informed Consent Form*[13]
From the ProAssurance Risk Management Sample Forms library, a sample form to assist you in creating a unique informed consent form for your practice

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CASE TWO:
Off-Label Use May Invite Surgical Technique Scrutiny

For the plaintiff to prevail in a malpractice case, the following elements of negligence must be proven:

- There must be a physician-patient relationship for the patient to establish a duty to provide care.
- The physician must have breached that duty and thus failed to meet the standard of care.
- The provider's breach of duty must have caused the patient harm.
- The plaintiff must establish damages as a result of the injury.

The standard of care is established in court by the testimony of expert witnesses and is the yardstick by which the defendant-physician's conduct is measured by the jury. In most jurisdictions, a doctor has a legal duty to provide a patient with the type and level of care that a prudent, similarly trained, and competent healthcare professional would provide. Expert witnesses testify on behalf of plaintiff and defendant, and then it is left up to the jury to decide if the standard of care was met. We often use expert reviewers at the beginning of a claim to gauge our insured's position and determine defensibility. The following case illustrates how the off-label use of a medical product intra-operatively may open the door for surgical planning and technique to be scrutinized.

Consider what may ultimately be scrutinized in the surgical planning process as the details of this case unfold.

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A 34-year-old female with a history of chronic back pain presented to an orthopedic surgeon. She explained that she had been in two separate motor vehicle accidents, most recently one year prior to the visit. She had attempted conservative therapy with NSAIDs, opioids, steroid injections, and physical therapy for the past few years, but her symptoms persisted. She described low back pain with radiation into her right hip but denied numbness, tingling, or weakness. MRI of the lumbar spine revealed a large disc herniation at L4/5.

The patient was offered a transforaminal lumbar interbody fusion (TLIF) surgery to address her symptoms. Documentation of the informed consent discussion revealed that the physician reviewed the planned procedure and discussed the risks of the procedure. The patient signed a consent for a TLIF at L4/5 with use of bone morphogenetic protein (BMP).

The patient underwent the procedure without complication. She was seen for follow-up at two weeks, and she complained of dull back and right leg pain. She was seen again for follow-up at three months postoperative and explained her right leg pain was much worse. A postoperative MRI was obtained and revealed scar tissue. The patient was referred to pain management for a spinal cord stimulator trial, but this failed to provide symptom relief.

The patient sought a second opinion from a neurosurgeon. In review of her three-month, six-month, and one-year post-op x-rays she was noted to have prolific bone formation where the BMP was placed intraoperatively, now encroaching on her nerves. The neurosurgeon discussed additional surgical options with the patient to address her new symptoms. He explained the possible challenges he may encounter intraoperatively due to the bony overgrowth. He added that additional surgery was an option, but the recovery would be lengthy and may not improve her symptoms. He also explained the increased risk of complications such as dural tears depending on the exact location of the BMP, which he could not fully visualize until the surgery. For these reasons she decided to hold off on further surgery and pursue more conservative therapies.

The patient pursued a claim against the operating surgeon for improper use of BMP, failing to explain the intended use of BMP was off-label, and for failure to obtain proper informed consent for use of BMP.

DISCUSSION

Expert reviewers felt that the physician met the standard of care in the informed consent process based upon his documentation. This reflected an explanation that BMP was approved for use in the cervical spine but not yet approved for use in the lumbar spine. Documentation reflected that the patient agreed to and understood that BMP would be used off-label during her surgery to promote bone growth and aid in the ultimate bony fusion. And finally, the informed consent listing the plan for TLIF with use of BMP was signed by the patient.

Expert reviewers were unsupportive on the decision to proceed with a spinal fusion surgery in this young female, opining that a less invasive surgery would have sufficed to address her symptoms and thus not required the use of BMP. Additionally, experts agreed that the manner in which the BMP was utilized was below the standard of care as evidenced by the migration and unwanted bone growth. BMP must be used very carefully in a contained manner to avoid this complication.

Further complicating the case were documented accusations against the BMP manufacturer for paying kickbacks to physicians who would agree to use it. There were concerns about the optics of this considering that multiple experts opined a fusion surgery was overly aggressive. This would put the plaintiff's attorney in a good position at trial. The attorney could paint a picture of a physician performing an unnecessary invasive procedure, which is not only a major ethical violation, but also could subject the physician to criminal or medical board actions.[14] Given these concerns, the case was settled with a payment to the patient.

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RISK REDUCTION STRATEGIES

When contemplating recommending the use of a medical product off-label, consider the following risk reduction strategies:

- Select a medical product that is FDA approved for the intended use whenever possible to ensure the safety and quality of the product. Encourage patients with endless choices to do the same.
- Ensure you have the knowledge, skill, and thorough understanding of the medical product as labeled prior to considering off-label use.
- Remember these basic healthcare ethical principles to help ensure safe prescribing practices:
  - **Beneficence** (acting for the patient's good) and **nonmaleficence** (doing no harm) will help to ensure you are meeting the standard of care as you weigh risks versus benefits for your patients.
  - **Respecting autonomy** (a patient's right to make their healthcare decisions) underlies the informed consent process and is vital to ensuring patients understand and accept risks associated with using medications potentially off-label.
  - **Justice** (equitably distributing healthcare resources among patients and otherwise treating them fairly) is useful for problem-solving in healthcare rationing situations. Have a plan to mitigate the impact of shortages and ensure continuity of care for affected patients.

ADDITIONAL RESOURCES

FDA: *Frequently Asked Questions about Labeling for Prescription Medicines*[15]
FDA's answers to healthcare professionals' most frequently asked questions about drug labeling

FDA: *BeSafeRx: Your Source for Online Pharmacy Information*[16]
Part of the FDA's BeSafeRx campaign, a link that can be shared with patients to help them learn about how to safely buy prescription medicines online

ProAssurance "2 Minutes: What's the Risk?" Video: *Off-Label Prescribing*[17]
A short video explaining the complex considerations that require careful evaluation to ensure that off-label prescribing is the right choice for your patient

ProAssurance *Claims Rx*: *Clinical Ethics and Risk Management: Patient Well-Being Wins the Day*[18]
An article exploring ethical issues in claim cases that includes excerpts from an interview with Dr. Lea Brandt, Director of the University of Missouri Center for Health Ethics

PRODUCTS LIABILITY: ARE YOU IN THE CHAIN OF MANUFACTURE?

Cornell's Legal Information Institute defines products liability as "the liability of any or all parties along the chain of manufacture of any product for damage caused by that product."[19] When damage is caused to a patient by a product, anyone in the chain can potentially be held liable. This includes the manufacturer at the top of the chain all the way down to the physician at the bottom of the chain who recommends or uses the product on the patient.

Medmarc, part of ProAssurance Group, provides products liability insurance to the life sciences industry. This primarily includes the manufacturers and distributors of medical technology and pharmaceutical products. Products liability cases provide insight to the public about what types of injuries can be caused by medical products. The following case example was supplied by Medmarc, and it reminds us that while off-label use of medical products is legal, promoting off-label use without sufficient warnings is not.

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CASE THREE:

Manufacturer Fails to Warn about Dangers of Off-Label Device Use

According to Zuhal Reed, a senior staff attorney at Medmarc, “Medical device manufacturers and healthcare providers must navigate the complex landscape of off-label use to minimize legal risks and ensure patient safety.” She further notes, “While off-label use is legal, it can pose significant challenges for manufacturers, especially when it comes to balancing the need to warn about foreseeable off-label uses without inadvertently engaging in off-label promotion.”

The case below, provided by Medmarc, illustrates how a medical device manufacturer failed to manage these challenges, leading to severe consequences for patients. This example underscores the critical importance of transparent communication and the responsibility to prioritize patient safety above market expansion.

Contemplate how physicians may be vulnerable to medical malpractice liability related to defective medical products as this case unfolds.

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XYZ Medical Devices, a prominent manufacturer, produced a pain pump approved by the FDA for delivering pain medications into the epidural or intrathecal space, primarily for managing chronic pain or postoperative discomfort. The device was used widely for these approved purposes. However, in an effort to expand its market reach, XYZ began promoting the potential for off-label use in orthopedic procedures, particularly for direct infusion into joint spaces. This off-label use was not approved by the FDA and posed significant risks, including cartilage damage—a condition known as chondrolysis.

Several patients suffering from joint pain were treated with XYZ's pain pump. Their physicians, influenced by off-label marketing and the potential benefits of localized pain relief, used the device to infuse pain medication directly into joint spaces. Despite the manufacturer's knowledge of the risks associated with such use, XYZ failed to warn physicians and patients adequately about the potential for severe cartilage damage.

Over time, the patients began experiencing serious complications, including rapid and irreversible cartilage loss, which led to chondrolysis—a painful condition that often necessitates joint replacement surgery. These outcomes severely impaired the patients' quality of life, leaving them with permanent disabilities.

A group of patients who developed chondrolysis after being treated with the pain pump filed a lawsuit against XYZ Medical Devices. The plaintiffs argued that the manufacturer had prioritized market expansion over patient safety by promoting the off-label use of the device in joint spaces without providing sufficient warnings about the associated risks. They claimed that XYZ Medical Devices had a duty to inform healthcare providers of the dangers of using the device in an off-label manner, particularly when it involved direct joint infusions.

The lawsuit alleged that XYZ was aware of the risks but chose not to act, neglecting their responsibility to safeguard patient health. The plaintiffs contended that the company's failure to provide explicit warnings led directly to their injuries.

DISCUSSION

The court ruled in favor of the plaintiffs, finding that XYZ Medical Devices had indeed neglected its duty to warn about the risks of off-label use in joint spaces. The court concluded that the manufacturer's actions—promoting off-label use without sufficient warnings—contributed to the patients' development of chondrolysis.

The judgment emphasized that XYZ Medical Devices had failed to strike an appropriate balance between expanding their market and ensuring patient safety. The court held that the manufacturer's negligence in adequately warning about the severe risks associated with off-label use in joints directly resulted in the plaintiffs' injuries. As a result, the court awarded substantial damages to the affected patients, holding XYZ Medical Devices accountable for the long-term consequences of the plaintiffs' condition.

WHEN THE DUTY TO WARN TRANSFERS TO THE PHYSICIAN

Generally when the use of a medical product results in a patient injury, multiple liability principles may be at play. If the patient's injury is a direct result of a defective product due to design, manufacturing, or marketing, this tends to fall under product liability. Marketing defects range from failing to provide adequate warnings as illustrated in the previous case, failing to provide proper instructions for use, or product labeling that does not sufficiently caution consumers about potential associated risks.[20]

However, when the manufacturer supplies sufficient information along with the transfer of the medical product to the treating physician, the duty to warn the patient typically also transfers to the physician who becomes the "learned intermediary."[21] The basis for this is that physicians ultimately make the treatment decision with sufficient awareness of the medical product risks and an understanding of the unique patient's clinical picture. This can shift causation from the medical product's defect to the physician's breach in meeting the standard of care, and thus establish physician negligence supporting medical malpractice.

Ensuring patients are fully informed about their medical condition, treatment options, and risks related to their treatments utilizing the Agency for Healthcare Research and Quality's (AHRQ) SHARE approach can help to ensure the physician's duty to warn is met. This approach allows for meaningful dialogue between the physician and patient to establish a clear understanding of the patient's goals.[22] Adopting this approach during the informed consent process helps to ensure physicians review both known and unknown risks related to use of medical products and equips patients with the ability to make an informed decision.

The SHARE approach can be extremely useful in situations where physicians are forced to offer non-FDA-approved treatments to their patients such as during shortages, supply chain issues, or during public health emergencies. In each of these situations it is vital that patients understand their options and the physician's decision-making process, and play an active role in accepting the unknown risks related to treatment. Thorough documentation of these efforts can strengthen defensibility of a claim should a future lawsuit arise related to risks that were unknown at the time of offering the treatment.

RISK REDUCTION STRATEGIES

Consider the following strategies to reduce risk of liability when medical products used or recommended to patients during your care lead to harm:

- Ensure a full understanding of labeling, instructions, and FDA-approved intended uses of the product prior to adopting or recommending a new medical product to patients.
- Encourage patients to review medication guides, patient package inserts, and instructions for use from the FDA that accompany their medication prescriptions.
- When considering the potential unapproved uses of approved medical products, review scientific or medical journal publications and clinical reference resources.
  - While pharmaceutical companies cannot market off-label use, they can supply these types of resources upon request.
- During shortages or supply chain issues, vigilantly monitor status to increase your ability to select an alternative that is currently available. Discuss this with your patients.
- Be sure that you relay known or possible warnings related to the use of medical products you recommend to your patients while considering their unique clinical picture.
- Adopt AHRQ's five-step SHARE approach to ensure shared clinical decision-making:[22]
  - **Seek** your patient's participation
  - **Help** your patient explore and compare treatment options
  - **Assess** your patient's values and preferences
  - **Reach** a decision with your patient
  - **Evaluate** your patient's decision

ADDITIONAL RESOURCES

AHRQ: *The SHARE Approach*[22]
An education and training tool for clinicians to aid in the inplementation of the SHARE approach into their practices

Journal of the American College of Cardiology: *Off-Label Use vs Off-Label Marketing*[23]
An article highlighting problems with off-label marketing by manufacturers and discussing steps that clinicians can take to avoid the risks associated with participating in off-label marketing

FDA: *FDA Drug Shortages*[24]
Searchable database for clinicians to monitor drug shortages and discontinuations reported to the FDA

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CONCLUSION

The use of non-FDA-approved medical products and approved products used off-label is common and sometimes the best option for patients. Use of these can lead to life-saving care but can also inadvertently result in patient harm. It is imperative that physicians balance the known and unknown risks with the potential benefits based on the patient's unique clinical picture. Physicians should take an evidence-based approach whenever possible to support their clinical decision-making and ensure safe care. By communicating effectively and involving patients through shared decision-making, the risk of patients pursuing claims if an unanticipated outcome occurs related to use of products that are either not FDA approved, or are being used off-label, can be reduced. If a claim is pursued, documentation of the evidence-based clinical decision-making can support adherence to healthcare ethics, and a thorough informed consent process can improve defensibility.

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ENDNOTES

The documents referenced in this article, along with many other risk management resource documents and past editions of *Claims Rx*, are available by calling Risk Management at 844-223-9648 or by email at RiskAdvisor@ProAssurance.com.

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