# Understanding On-Label, Off-Label, and Unapproved Products

Be a savvy consumer.

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The numerous requirements to legally market a medical device, drug, biologic, or combination thereof in the United States are meant to reassure consumers that these medical products are safe and that the scope of their effectiveness is understood. The FDA has jurisdiction and oversight of drugs and medical devices in the United States, including their clinical investigation, sale, distribution, advertising (for prescription drugs and restricted medical devices),[1] labeling, and importation. The regulatory road to market can be complex and is not always well understood, which can lead to legal risk for the companies that develop and manufacture products and for the health care providers who prescribe or recommend products.

## UNDERSTANDING MARKET AUTHORIZATION AND CLINICAL TRIAL REGULATIONS

**Market authorization.** A company or an individual must receive approval from the FDA to legally market a drug product[2] and approval or clearance from the FDA to market a medical device in the United States.[3] A company or an individual may be granted approval, clearance, or a license from the FDA to market a combination product based on the primary mode of action of the drug or device (ie, product). The FDA assigns combination products to a center that will have primary jurisdiction for its premarket review and regulation based on a determination of the primary mode of action of the combination product.

Regulatory authorization is specific to the proposed use of the product. Before authorization, the product must be studied by the party seeking market approval and shown to be safe and effective. This information is included in the product labeling or instructions for use (IFU). Use of the product consistent with the product labeling or IFU is referred to as *on-label*.

Once the FDA approves a medical product, health care providers generally may prescribe its use for a purpose outside the product labeling or IFU when they judge that it is medically appropriate for their patient. This is referred to as *off-label*. If a product has never been reviewed by the FDA and was never granted any market authorization, the product is *unapproved*. The use of an unapproved product is not off-label (there is no label) and very likely may be unlawful.

Another requirement of market authorization is that a product must be manufactured in accordance with good manufacturing practices (GMPs). GMPs help to ensure that medical products are consistently produced and controlled according to quality standards. The quality of the manufacturing of an unapproved product is unknown. Therefore, neither a consumer nor a health care professional using an unapproved product has any assurance that it was manufactured in accordance with GMPs, that it is safe, or that it will be effective. The failure to obtain FDA approval, licensure, or clearance of a medical product presents significant legal risks and liabilities to companies and individuals, and it jeopardizes the health and well-being of unsuspecting patients who use or receive treatment with the product.

**Clinical trials.** Permission from the FDA is required to legally conduct a clinical trial of a medical product that is intended for use in human subjects within the United States and that has never undergone regulatory review by the FDA. There are two types of applications, an investigational new drug (IND) and an investigational device exemption (IDE). An IDE is intended for significant risk devices that present a potential for serious risk to the health, safety, or welfare of a subject. Institutional Review Board approval of the study must occur for both IND and IDE applications; however, a clinical study involving a nonsignificant risk device requires Institutional Review Board approval only prior to initiation of the clinical study.

> "Since 2012, the FDA has notified nearly 3,500 physicians that their drug-purchasing practices may be illegal. In 2019, the FDA issued a warning letter to a doctor for illegally marketing an unapproved medical device. The US Department of Justice has prosecuted more than 95 corporations and individuals, including physicians, for criminal charges related to selling or receiving and administering unapproved drug products to patients."

## IMPORTATION AND PROHIBITED ACTS

**Importation.** Marketing encompasses not just the promotion of a product but also the movement of that product in commerce. The Federal Food, Drug, and Cosmetic (FD&C) Act prohibits the interstate shipment and importation of unapproved new drugs, including biologics. It also prohibits the importation of unapproved and uncleared medical devices.[4] Thus, the importation of new drugs or medical devices that lack FDA approval, licensure, or clearance—whether for personal use or otherwise—violates the FD&C Act. Similarly, medical devices imported or offered for import into the United States must comply with all applicable requirements related to medical device approval or clearance, proper labeling, establishment registration and device listing, and GMPs.

Further, investigational products imported into the United States for study must have a valid IND or IDE. Foreign manufacturers whose drugs or medical devices are imported or offered for import into the United States are required to register their establishments and list all drugs and medical devices that they have in commercial distribution in the United States.[5]

An unapproved drug or unapproved or uncleared medical device intended solely for tests in vitro or use in laboratory animals may be shipped (including import) to the United States if its labeling designates that it is not for use in human subjects and is only for use in laboratory research animals or for tests in vitro.[6] However, in the case of drug products, the person offering the drug for import must use due diligence to ensure that

## CASE IN POINT

The State of Texas brought suit against a women's health care practice that had sold and implanted unapproved intrauterine devices (IUDs) imported from Canada.[1] The lawsuit sought up to $20,000 in civil penalties for each violation and a court order requiring the clinic to sell only FDA-approved IUDs.

1. State v Women's Integrated Healthcare, P.A., et al, 352-248912-10 (Tex. Dist. Ct. 2010).

the individual receiving the imported investigational drug is regularly engaged in conducting such tests and that the shipment of the drug will be used only for tests in vitro or in animals for laboratory research.

**Prohibited acts.** A drug or medical device is misbranded if its labeling is false or misleading,[7] for example if a drug or medical device that is labeled for use in research animals is used in humans. The receipt in interstate commerce of a drug or medical device that is misbranded and the delivery or offer of delivery of the same for pay or otherwise is prohibited under the FD&C Act.[8] Those who commit a prohibited act may be subject to criminal and civil penalties and other actions.[9]

## HOW THIS APPLIES TO PHYSICIANS

Since 2012, the FDA has notified nearly 3,500 physicians that their drug-purchasing practices may be illegal. In 2019, the FDA issued a warning letter to a doctor for illegally marketing an unapproved medical device.[10] The US Department of Justice has prosecuted more than 95 corporations and individuals—including physicians—for criminal charges related to selling or receiving and administering unapproved drug products to patients.[11] These criminal convictions have resulted in incarceration, millions of dollars of fines, and debarment, which would preclude the debarred party from providing services in any capacity to a person with an approved or pending drug product application with the FDA.[12] Physicians who import an unapproved product and use the product in the treatment of federal health care beneficiaries also may be alleged to have violated the federal False Claims Act.[14]

States have increased their attention on the purchase of unapproved and/or uncleared medical products and devices from sources outside the United States for use in unknowing patients (see *Case in Point*). Some states have laws that mirror the national FD&C Act with provisions that prohibit the purchase or administration of drugs and medical devices that are not approved or cleared by the FDA.[13]

## CONCLUSION

Given the significant potential penalties and patient risks associated with the use of unapproved medical drugs and devices, physicians must be savvy consumers of the products that they purchase or recommend. It is wise to do your diligence on any questions or concerns regarding a product's authorization status. ■

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1. 21 U.S.C. § 352(n), (q), & (r).
2. 21 U.S.C. § 355(a).
3. 21 U.S.C. §§ 360e(a) & 360(k).
4. 21 U.S.C. § 331(a) & (d); 21 U.S.C. §§ 350(o) & 351(f)(1)(B); 42 U.S.C. § 262(a).
5. 21 C.F.R. §§§ 207.17(a), 207.41, and 807.40(a).
6. 21 C.F.R. §§ 312.160(a) & 812.5(c).
7. 21 U.S.C. § 352(a).
8. 21 U.S.C. § 331(c).
9. 21 U.S.C. § 331(d).
10. Warning letter. US Food and Drug Administration. February 13, 2019. Accessed March 12, 2019. https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm631059.htm
11. FDA notice to physicians. US Food and Drug Administration. Accessed March 12, 2019. https://www.fda.gov/downloads/Drugs/ResourcesForYou/HealthProfessionals/UCM529697.pdf
12. Albert Poet: Debarment order. Federal Register. March 3, 2011. Accessed February 14, 2019. https://www.fda.gov/ICECI/CriminalInvestigations/ucm586183.htm and https://www.federalregister.gov/documents/2011/03/03/2011-4778/albert-poet-debarment-order
13. Texas Health & Safety Code §§ 431.021 & 431.111.
14. Board certified ophthalmologist agrees to civil fraud settlement in Medicare fraud investigation. News Release. United States Department of Justice. September 24, 2018. Accessed September 28, 2020. https://www.justice.gov/usao-edny/pr/board-certified-ophthalmologist-agrees-civil-fraud-settlement-medicare-fraud