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Navigating the Gray Area: Understanding the Legalities of Off-Label Drug Use

Analysis by Dr. Joseph Mercola | June 05, 2024

STORY AT-A-GLANCE

- In the U.S., 1 in 5 prescriptions are written for an off-label use; this protects doctors' ability to freely treat patients, and patients' ability to use all available treatments after making an informed decision
- FDA regulations require all over-the-counter (OTC) progesterone products to be labeled for topical and cosmetic use only
- As a result, manufacturers are unable to promote transmucosal application of these products without reclassifying them as new drugs, even though it is perfectly legal for physicians to prescribe it that way
- I do not recommend transdermal progesterone, as your skin expresses high levels of 5-alpha reductase enzyme, which causes a significant portion of the progesterone you're taking to be irreversibly converted primarily into allopregnanolone and cannot be converted back into progesterone
- This is why I recommend applying progesterone transmucosally — on your gums — as then it is absorbed directly into the bloodstream

In the U.S., 1 in 5 prescriptions are written for an off-label use.[1] This means that a physician is prescribing a medication for a purpose that has not been officially approved by the U.S. Food and Drug Administration (FDA). While the FDA approves drugs for specific uses, physicians can legally prescribe them for other uses that they deem medically appropriate.

This practice is common and often based on emerging evidence, clinical experience or guidelines from professional medical societies. While sometimes this allows medications to be overused or misused, it also protects doctors' ability to freely treat patients, and patients' ability to use all available treatments after making an informed decision.

As it relates to progesterone — one of **four hormones** I believe most adults can benefit from — the route of administration is particularly important and influences its effectiveness.

Unfortunately, if applied transmucosally, which is the preferred method, the FDA views this as turning the supplement into a drug. So, due to this gray area, over-the-counter progesterone products cannot list transmucosal application on their label, even though it is perfectly legal for physicians to prescribe it that way.

Legal Technicalities Block Best Route of Progesterone Administration on Labels

In the complex landscape of modern medicine, off-label drug use represents a significant gray area that both empowers and challenges health care providers and patients. It's important to understand that while the FDA regulates the approval and marketing of pharmaceuticals, it does not control the practice of medicine.

This regulatory framework allows physicians the latitude to prescribe medications for unapproved uses, a practice known as off-label prescribing. Off-label use can be crucial for patient care, offering alternative treatment options when standard therapies fail or are unavailable.

For instance, a physician might use a hormone like progesterone transmucosally despite its primary approval for other routes of administration. Such flexibility is vital in tailoring treatments to individual patient needs and advancing clinical practice based on emerging evidence and experience.

However, people who could benefit from transmucosal administration of drugs like progesterone might not be empowered with this information due to FDA regulations. These regulations require all over-the-counter (OTC) progesterone products to be labeled for topical and cosmetic use only.

As a result, manufacturers are unable to promote the internal use of these products without reclassifying them as new drugs, which would necessitate a lengthy and costly approval process.

This regulatory environment can leave you uninformed about potential benefits and alternative applications of medications. For example, a person seeking effective hormone therapy might be unaware that transmucosal progesterone could be a viable option, as this information is not widely promoted or available due to regulatory constraints. Consequently, patients may miss out on treatments that could significantly improve their quality of life.

Why I Recommend Applying Progesterone to Your Gums, Not Your Skin

Transdermal and transmucosal administration are two methods of delivering medication through different types of body tissues. Transdermal administration involves applying medication directly to the skin. The drug is then absorbed through the skin layers and into the bloodstream over time.

Transmucosal administration involves applying a substance to mucous membranes, such as those found in the mouth. The compound is absorbed through the mucosal tissues and directly enters the bloodstream. The FDA considers the route of administration significant in determining whether a progesterone product is considered a new drug. The FDA views transmucosal applications as distinct from topical applications and subject to different regulatory requirements.

However, I do not recommend transdermal progesterone, as your skin expresses high levels of 5-alpha reductase enzyme, which causes a significant portion of the

progesterone you're taking to be irreversibly converted primarily into allopregnanolone and cannot be converted back into progesterone.

This is why I recommend applying progesterone transmucosally — on your gums — as then it is absorbed into the bloodstream directly rather than bypassing first pass metabolism in the liver that converts it into useless metabolites. As mentioned, when progesterone is used transmucosally on your gums as I advise, the FDA believes that somehow converts it into a drug and prohibits any company from advising that on its label.

While some have expressed concerned that the label on their product says it is for skin use only, please understand that this is most likely for the reasons just stated — this is not for your protection; it is to protect the drug company's cash flow. Applying the progesterone to your gums is the ideal route of administration and is a perfectly legal off-label use of progesterone.

In this case, progesterone is a natural hormone, not a drug, and is very safe even at high doses. This is unlike synthetic progesterone called progestins that are used by drug companies, but frequently, and incorrectly, referred to as progesterone, which are dangerous and should never be used by anyone.

Tips for Proper Progesterone Administration

Before you consider using progesterone it is important to understand that it is not a magic bullet and you get the most benefit by implementing a Bioenergetic diet approach that allows you to effectively burn glucose as your primary fuel with backing up electrons in your mitochondria that reduces your energy production. My new book coming out shortly about Cellular Health covers this process in great detail.

Once you have dialed in your diet, an effective strategy that can help counteract **estrogen excess** is to take transmucosal progesterone (not oral or transdermal), which is a natural estrogen antagonist. As mentioned, progesterone is one of only four

hormones I believe many adults can benefit from. (The other three are thyroid hormone T3, DHEA and pregnenolone.)

As a general recommendation, I recommend taking 25 to 50 mg of bioidentical progesterone per day, taken in the evening one hour before bed, as it can also promote sleep. For optimal bioavailability, progesterone needs to be mixed into natural vitamin E. The difference in bioavailability between taking progesterone orally without vitamin E and taking it with vitamin E is 45 minutes versus 48 hours.

You can make your own by dissolving pure USP progesterone powder into one capsule of a high-quality vitamin E, and then rub the mixture on your gums. Fifty milligrams of powdered progesterone is about 1/32 teaspoon.

You can purchase pharmaceutical grade bioidentical progesterone as Progesterone Powder, Bioidentical Micronized Powder, 10 grams for about $40 on many online stores like Amazon. That is nearly a year's supply, depending on the dose you choose.

Do not use synthetic vitamin E (alpha tocopherol acetate — the acetate indicates that it's synthetic). Natural vitamin E will be labeled "d alpha tocopherol." This is the pure D isomer, which is what your body can use.

There are also other vitamin E isomers, and you want the complete spectrum of tocopherols and tocotrienols, specifically the beta, gamma, and delta types, in the effective D isomer. As an example of an ideal vitamin E you can look at the label on our vitamin E in our store. You can use any brand that has a similar label.

If you are a menstruating woman, you should take the progesterone during the luteal phase or the last half of your cycle, which can be determined by starting 10 days after the first day of your period and stopping the progesterone when your period starts.

If you are a male or non-menstruating woman you can take the progesterone every day for four to six months and then cycle off for one week. The best time of day to take progesterone is 30 minutes before bed as it has an anti-cortisol function and will increase GABA levels for a good night's sleep.

Does the FDA Want the Power to Regulate the Practice of Medicine?

The 2023 omnibus appropriations bill — a 4,155-page tome involving $1.7 trillion in spending — included 19 lines that would give the FDA the power to ban off-label use of approved medications. In a commentary for the Wall Street Journal, Joel Zinberg wrote:[2]

> *"Physicians routinely prescribe drugs and employ medical devices that are approved and labeled by the Food and Drug Administration for a particular use. Yet sometimes physicians discern other beneficial uses for these technologies, which they prescribe for their patients without specific official sanction.*
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> *The new legislation amends the Food, Drug and Cosmetic Act, or FDCA, to give the FDA the authority to ban some of these off-label uses of otherwise approved products. This unwarranted intrusion into the physician-patient relationship threatens to undermine medical innovation and patient care."*

"The new provision was enacted at the FDA's urging," Zinberg says,[3] in response to a 2021 legal ruling that limited the FDA's power to meddle with the practice of medicine. In March 2020, the FDA banned the use of electric shock devices for particular uses, namely to treat patients engaging in self-harm or aggressive behaviors that could harm others.

The devices are FDA approved, and while the FDA banned their use for certain contexts, it still allowed them to be used for smoking addiction and other purposes.[4] This led to a lawsuit — Judge Rotenberg Education Center v. FDA — in which the Judge Rotenberg Education Center, a school for people with severe behavioral and intellectual conditions, sued the FDA over the ban.

The court ruled in the school's favor, stating that the FDA's ban violated federal law because it interfered with health care practitioners' authority to practice medicine. As it stands, the FDA does not have the power to ban medical devices for a particular use.

As it stands, Section 360f of the FDCA only gives the FDA authority to ban a medical device if it poses "an unreasonable and substantial risk of illness or injury." It can ban the device outright, but it can't pick and choose when it can and can't be used.

"Barring a practitioner from prescribing or using an otherwise approved device for a specific off-label indication would violate another FDCA section, which bars the FDA from regulating the 'practice of medicine,'" Zinberg says.[5] Further, according to a proposed rule in the March 26, 2024 Federal Register:[6]

> *"The Food and Drug Administration (FDA, the Agency, or we) is proposing to ban electrical stimulation devices (ESDs) intended for self-injurious behavior (SIB) or aggressive behavior (AB). FDA has determined these devices present an unreasonable and substantial risk of illness or injury that cannot be corrected or eliminated by labeling.*
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> *This proposal follows a court decision vacating a prior ban and amendment to the Federal Food, Drug, and Cosmetic Act clarifying our authority to ban a device for one or more intended uses. This action, if finalized, will mean ESDs for SIB and AB are adulterated and not legally Marketed."*

Health Care Decisions Belong Between You and Your Doctor

When the FDA, and by proxy Big Pharma, oversteps its regulatory boundaries, it puts them at the helm of powerful health care decisions that should be made on an individual, personalized level between a patient and their health care provider. During the pandemic, it became clear how patients suffer when health agencies are allowed to **dictate what medications** doctors are allowed to prescribe to their patients.

The FDA's refusal to allow transmucosal application to be listed on OTC progesterone labels is another example of industry stepping in the way of the practice of medicine. It's safe to rub progesterone on your gums — and doing so is the preferred application.

Sources and References

- [1, 2, 3, 5] The Wall Street Journal January 12, 2023
- [4] CNN July 16, 2021
- [6] Federal Register March 26, 2024, Vol. 89, No. 59, 20882