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Sailing the Straits of Approval: The Nature of FDA Approval and Its Implications for Surgeons

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Products approved by the US Food and Drug Administration (FDA) for one use are often put to other uses. This practice, known colloquially as “off-label usage,” is driven by many forces—from physician interest to patient demand. It is legal [1], although promotion of off-label use by manufacturers is not [2]. Some off-label use is supported by a sound evidence base [3,4], but as cited by Radley and colleagues [5], “Most [off-label use] occurs without scientific support.”

Off-label use of products is common in facial plastic surgery [6,7]. Physicians began using injectable botulinum toxin for amelioration of facial rhytides long before creation and FDA approval of the same material tested and approved for this purpose (Botox). Even Botox is commonly used off-label, because it is approved only for the “...temporary treatment of moderate to severe frown lines between the brows in people ages 18–65.” Although we are well beyond the days in which lubrication grade silicone was autoclaved and used as injectable filler, facial plastic surgeons continue to use a wide variety of materials for implantable or injectable contour augmentation despite a total lack of scientific proof of safety or efficacy.

The issues before facial plastic surgeons regarding off-label use of products are clear and important, and they include the following questions:

- Is off-label use of anything justified without a base of supporting evidence?
- Is there a need to disclose off-label use to patients?
- Is there a need to disclose a lack of clinical evidence supporting that use?
- Is prudent medical judgment sufficient justification for such use?
- What are the medicolegal risks of off-label prescribing?
- Is prudent medical judgment sufficient defense against allegations of negligence resulting from such use?
- What scientific issues surround off-label use?
- What ethical considerations surround off-label use?

The US Food and Drug Administration

The US FDA has exercised regulatory function and power over human drugs and biologics, complex medical devices, food and color additives, infant formulas, and animal drugs since the passage of the Federal Food and Drugs Act of 1906. Its jurisdiction encompasses most food products (other than meat and poultry),

human and animal drugs, therapeutic agents of biologic origin, medical devices, radiation-emitting products for consumer, medical, and occupational use, cosmetics, and animal feed. These items currently account for 25 cents of every dollar spent by US consumers, giving the US FDA enormous influence over life in this country.

The US FDA focuses regulatory and other control efforts on market entry rather than physician prescribing. This leaves off-label use to the judgment and discretion of the physician.

As facial plastic surgeons, we use and prescribe many products subject to US FDA regulation. To comply with the regulations governing activities subject to US FDA oversight, we must know and understand the spectrum of US FDA regulations and activities as it applies to us. The US FDA is charged by law with many functions, among them the evaluation and approval for marketing of drugs and medical devices, receiving and evaluating reports of adverse reactions to medical devices, postmarket monitoring of implants and other devices that pose a serious health risk, recall authority over medical devices, and certification and annual inspection of mammography facilities.

The US FDA function of most relevance to this discussion is approval of a device or substance for marketing. Such approval is given for specific indications after documentation of sufficient safety and efficacy to meet US FDA requirements or of “substantial equivalence” to a similar device or substance that is already approved (a “510k” approval).

Discussion

The use of medical products and devices approved by the US FDA for another purpose is known as off-label use. It is neither prohibited nor regulated, and the US FDA addresses it clearly with the following statement [8]:

“Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects.

Use of a marketed product in this manner when the intent is the “practice of medicine” does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which

the product will be used may, under its own authority, require IRB review or other institutional oversight.”

This use must be distinguished from “investigational use” of approved marketed products, which is described by the US FDA in the same document as “use of an approved product in the context of a clinical study protocol.” If the principle intent of investigational use is determination of safety and efficacy, submission of an Investigational New Drug Application or Investigational Device Exemption is required unless all of the following six criteria are met:

- (1) It is not intended to be reported to the US FDA in support of a new indication for use or to support any other significant change in the labeling for the drug.
- (2) It is not intended to support a significant change in the advertising for the product.
- (3) It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- (4) It is conducted in compliance with the requirements for Institutional Review Board review and informed consent.
- (5) It is conducted in compliance with the requirements concerning the promotion and sale of drugs.
- (6) It does not intend to invoke 21 CFR 50.24 (which governs procedures performed under emergency circumstances when informed consent is not obtainable).

Moral, ethical, and legal concerns

Although off-label use is neither illegal nor inherently wrong, there is a common misperception that it is one or both—and consumer health Web sites do nothing to counter this. For example, an article found on “The Doctor Will See You Now” [9] introduces the concept of off-label use as “...also known as unapproved use...” Although it also clearly and correctly states that off-label use by itself does not constitute malpractice, the consumer easily could be led to believe the opposite from such Web sites (many of which seem to have been created for the sole purpose of generating allegations of negligence based on off-label use).

The lay press also takes notice of off-label use. The Washington Post [10] thought Radley's publication on off-label use in the Archives of Internal Medicine important enough to run an article on the subject.

The drive for this coverage is stated by the author to have been Radley's conclusion that "Off-label medication use is common in outpatient care, and most occurs without scientific support."

Patient considerations

Prudent advice might best come from simple paraphrasing of the US FDA's own statements about off-label use. If physicians use a product for an indication not in the approved labeling, they have the responsibilities to

- Be well informed about the product
- Base its use on firm scientific rationale and sound medical evidence, if available
- Maintain records of the product's use and effects
- Carry out good medical practice
- Use good judgment
- Consider the best interests of the patient before all else

Patient demand for treatment continues to stimulate off-label use. Patients profess not to care about the US FDA status of a treatment or product they want if they believe it will enhance their appearance. In the experience of this author, however, virtually none recalls saying or believing this in the face of suboptimal results. This attitude mandates consideration and discussion of adverse outcomes and responsibility for their management before treatment. Basic questions such as who will pay for management of complications must be answered. This information is especially necessary for patients without health insurance and for patients whose health insurance specifically excludes coverage for complications of cosmetic procedures.

If a patient relies on the judgment and opinion of a facial plastic surgeon that off-label use of a product poses low risk and high likelihood of success and there is no published evidence to support that belief and opinion, allegations of negligence over an adverse outcome will be more difficult to counter than if there is strong evidence of frequent success.

The euphemistic term "innovative off-label use" has been defined as "prescribing with reasonable rationale for use, but insufficient evidence to allay safety, efficacy, and cost-effectiveness concerns" [11]. Clinicians are documented to have "discovered" approximately half of 143 innovative off-label uses of medication investigated in a recent study [12], and this number is at the low end of the generally reported range of observation of this phenomenon. Given the

paucity of treatments representing the sole option for management of a given problem, one must question the wisdom and ethics of embarking on novel off-label use without Institutional Review Board supervision.

There are active attempts to regulate or otherwise control innovative off-label use, notably work that is ongoing at the University of Pittsburgh. From a recent publication discussing this problem and their solution to it, Ansani and colleagues [11] described a "...multidisciplinary group [that] developed a policy and process to regulate innovative off-label medication use that standardizes formulary review, maximizes peer expertise input, and minimizes institution liability by evaluating the effectiveness of use, promoting evidence-based practices, and ensuring ethical obligations to patients and society."

Because professional liability claims may center on off-label use and the legality of off-label use is often based on patient consent [13], it seems clear that facial plastic surgeons should inform patients of off-label status whenever providing such treatment, especially if that treatment is a novel use of the product. This can be done in context, because many off-label uses are common and have a literature base for support. If recommended treatment lacks published support, however, it is in the best interest of the facial plastic surgeon to disclose this information to the patient before treatment and to document the interaction.

Many mainstays of therapy would be missing from the armamentarium of modern medicine without innovative off-label use. Facial plastic surgeons must temper the desire to innovate with the practical realities and ethical grounding of evidence-based practice, informed consent, and consideration of the overall best interests of patients. Complete and accurate documentation of off-label use and its outcomes is mandatory so that we can continue to advance the quality of care with the support and encouragement of the community.

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