ENDLESS AND ESSENTIAL:
THE TUG OF WAR OVER OFF-LABEL USE

Will the pendulum swing once again?

BY JAMES INCOLLINGO, MA, CONTRIBUTING EDITOR

In the beginning, there were no labels. Regulations were few, and no dedicated agency existed to enforce them. Healers were free to apply nearly any substance, technique, or device in their efforts to relieve the suffering brought on by injury and disease. At different times and in different places, their kits could include anything from incantations and blood-sucking leeches to debilitating or lethal doses of toxins such as mercury, lead, and uranium. Occasionally, patients benefitted from the medical interventions visited upon them.

With the advent of the scientific method and the subsequent vast improvements in the education, professionalization, and effectiveness of doctors, the days of bloodletting and snake oil began to wane. Even still, and with all our rigorously established and formalized research protocols, doctors cling tenaciously to the freedom, previously unfettered, to apply their individual creativity, experience, and even gut instinct when seeking to heal the afflicted. They value this freedom for one reason above all others: because it has generated, over the centuries, a bona fide bonanza of ingenious and sometimes paradigm-shifting health care innovations—IOLs and phacoemulsification, to name two.

Unfortunately, greedy quacks and reckless hacks remain with us, and those who will not be reined in by organized health care professionals have invited the strong arm of the law into the art and science of doctoring. With legislation such as the Pure Food and Drug Act of 1906 and the empowerment of the regulatory oversight behemoth known as the Food and Drug Administration, consumers were afforded, for the first time, significant protections against adulterated, toxic, or useless medications and devices. The institution of clinical phase trials to determine scientifically the safety and effectiveness of drugs and devices helped cull many dangerous, feckless, and ludicrous examples from the pharmacopeia. The tension that arose between regulators trying to protect the public and doctors trying to innovate was largely inevitable, and it continues today.

Labeling these parties competing forces would miss the mark, because ultimately, both doctors and medical regulators want the same things: safer, more effective treatments and better outcomes for patients. Physicians and regulators rely upon and assist each other in their missions, but they are also adversaries, based on their histories and specific methods. Cast starkly, a regulator wants everything done by the book, exhaustively tested, and thoroughly proven, whereas a doctor, while happy to use tested and proven treatments, wants the maximum freedom ethically possible to solve vexing medical problems when his or her bag of tested and proven solutions fails to help a patient.

In modern times, this tension between regulators and doctors plays out under the banners of *on label* (drugs or

AT A GLANCE

- Tension between regulators and doctors plays out under the banners of *on label* and *off label*. The arenas for the contest are medical journals and conferences, the offices of legislators and regulators, and perhaps of most consequence lately, the US federal court system.
- Whereas the pharma industry's ire is over hefty fines and marketing strictures, physicians focus on the chill that they feel has slowly descended over the free flow of accurate information in the wake of such regulations, backed as they are by the punitive power of the state. Some believe the crackdown and its downstream effects are hurting continuing medical education.
- In their endless quest for innovative cures and better treatments, bold clinicians will continue to walk the tightrope of off-label use over the chasm of potential disaster. They have to, because history has shown that the rewards are, on balance, worth the risk.

devices tested and approved for specific uses) and *off label* (those same drugs or devices prescribed by doctors for uses not fully tested and approved). The arenas for the contest are medical journals and conferences, the offices of legislators and regulators, and perhaps of most consequence lately, the US federal court system.

OFF-LABEL USE IS GOOD

The average patient might be shocked at the type and quantity of off-label usage, because it is widespread, thoroughly entrenched, and fundamental to the practice of modern medicine. It is the potential for harm that keeps regulators up at night.

Like most of his colleagues, New York-based corneal specialist and cataract surgeon Eric Donnenfeld, MD, strongly supports the role of off-label drug use in modern medicine. In an interview with *CRST*, the recent president of the American Society of Cataract and Refractive Surgery went so far as to declare, "The off-label prescription of medications is at the heart of medicine." He added that "medications are often approved for very limited indications, but through doctor evaluation and interaction with patients, new indications constantly emerge. These new indications are sometimes more important than the original indications that were approved by the FDA."

"Nonsteroidal [anti-inflammatory drugs (NSAIDs)] are indicated for inflammation, but they're not indicated for cystoid macular edema," Dr. Donnenfeld continued. "But, we regularly use [NSAIDs] for prophylaxis and the management of cystoid macular edema. Along similar lines, steroids are approved for inflammation commonly associated with surgery, but the FDA indications are for a very limited dosing pattern. For example, Durezol [difluprednate; Alcon] is only approved to be started 1 day after surgery, and it's not approved [for] use on the day of surgery. So, there are not only limits on what drugs can be used for but also the scheduling."

Medical devices exist under the same on-label/off-label system as medications. To illustrate, Dr. Donnenfeld pointed to IOLs: "They're approved for cataract surgery, but they're not approved for clear lens extractions. Likewise, [microinvasive glaucoma surgery] devices are only approved for use with cataract surgery, and using only one is approved, but clearly, we know that two gives better results than using one."

Off-label use is particularly common in treating maladies of the eye. According to Philadelphia-area ophthalmologist Cynthia Matossian, "We use antibiotic drops usually starting 1 to 3 days prior to cataract surgery and continue them in the immediate perioperative period. That is an off-label use of antibiotics. By doing so, we can decrease the risk of endophthalmitis, but there is no indication for it when you read the antibiotic product. They're mainly for bacterial conjunctivitis, and none of them says 'for cataract surgery and endophthalmitis prevention.' We do about 3.3 million cataract surgeries per year, and most of the time, an antibiotic is paired with cataract surgery."

She continued, "Another drug that we use is called AzaSite [Akorn], which is azithromycin ophthalmic solution. It's a very viscous drop that we use for the treatment of blepharitis, which is a chronic disease. So, we prescribe AzaSite in a very specific way, by rubbing the drops into the eyelashes and at the base of the eyelids every night, sometimes for months and months at a time. Again, it's a very off-label use for this product."

"In the case of epidemic keratoconjunctivitis or EKC, sometimes a product called Zirgan [ganciclovir; Bausch + Lomb] is used, which is designed to treat a herpes simplex dendrite on the cornea," Dr. Matossian said. "But, we often use Zirgan off label when patients develop subepithelial corneal infiltrate and epidemic keratoconjunctivitis, or we use Zirgan in some patients who have herpes zoster, called *herpes zoster pseudodendrite*. Because it's not the real herpes simplex dendrite, that's an off-label use of the product."

"Ophthalmologists knowingly use Zirgan, or azithromycin/Azasite, NSAIDs, and antibiotics off label on a regular basis," she said. "We do it because we believe it works, it's the standard of care, and we believe it helps reduce the risk of infection or [cystoid macula edema] in our patients. Otherwise, we wouldn't be doing it."

In a conversation with *CRST* Chief Medical Editor and second-generation Florida ophthalmologist, surgeon, and educator Robert Weinstock emphasized that off-label usage extends well beyond his areas of specific expertise. Like Dr. Donnenfeld, Dr. Matossian, and many others, Dr. Weinstock believes the entire enterprise of modern medicine depends upon this practice: "There are many, many medications across all specialties that, once approved by the FDA, are found by clinicians and patients to have benefits in other conditions, well outside of what they were originally tested for. Part of medicine is art. It's art and science, and that's why they call it 'practicing' medicine, because the practice of medicine involves trying things sometimes that are new. That's the only way medicine advances. Without taking medications that are available and approved and using them at a surgeon's or physician's discretion to try to do things they think may help, there would be no innovation and no advancement of medicine."

In this light, most doctors are comfortable with the fact that, each year across all the specialties, roughly one out of every five prescriptions is written for an off-label use. What worries them is that the free flow of information about it can sometimes be strangled by the very regulations, or regulatory atmosphere, intended to protect health care

> "The strictures and penalties have simply gone too far, whether or not violations are clearly evident."

consumers. As Dr. Matossian lamented, "We are hampered and constrained by the inability to freely, legally, and officially discuss these wonderful medications that we use in off-label ways, and there are so many that we use off label."

Although the impetus for the regulatory impulse is nearly universally accepted as legitimate, to many in the day-to-day, hands-on practice of the healing arts, the restrictive manifestations have lately become too burdensome and counterproductive. Not surprisingly, in our quasi-capitalist system of health care distribution, to those in the business of selling drugs and devices, the tendency can be to view profit-dampening regulation less as a necessary evil and more as just evil.

MARKETING, EDUCATION, AND FREE SPEECH

For decades now, the FDA has tightly regulated the sort of off-label information that a drug or device marketing representative can offer a physician, whether or not the doctor specifically requests to hear it. The noble intent is to prevent profit-hungry drug and device makers from misrepresenting the truth and promoting improper uses that may lead to unnecessary suffering or death. Overwhelmingly, doctors recognize the need for this type of regulation, and they welcome it, within reason.

From his base in Austin, Texas, refractive surgeon, author, lecturer, and Chief Medical Editor of *CRST* Steven Dell summed up the justification: "It stems from abuses, where a drug may be approved for one use, but a manufacturer encourages doctors to use their drug in an off-label capacity where the science has not substantiated it. They might anecdotally report that a particular doctor or some other opinion leader was using the drug in that capacity, and that was justification enough. I don't think that meets the FDA's criteria for establishing safe and effective use for a drug. I think the FDA's concerns are well founded, but if there is a preponderance of medical literature that backs up a particular form of use of a drug, we ought to have the freedom to hear about that from the manufacturers."

According to many doctors and pharmaceutical manufacturers, the strictures and penalties have simply gone too far, whether or not violations are clearly evident. Within just the past decade, pharmaceutical manufacturers have been fined more than $16 billion for off-label use promotion violations that they see as excessive at best and unconstitutional at worst.[1] For example, in 2009, Pfizer was assessed a $2.3 billion penalty for improperly promoting off-label uses for its pain reliever Bextra (valdecoxib). That same year, Eli Lilly was charged $1.42 billion for similar violations regarding its schizophrenia drug, Zyprexa (olanzapine). Ophthalmic giant Allergan felt the pinch in 2010 to the tune of $600 million over its promotion of Botox (onabotulinumtoxinA) for off-label uses such as pain, headache, and cerebral palsy. In 2012, GlaxoSmithKline took the cake (the one that nobody wants) by agreeing to pay a $3 billion penalty for fraud in its marketing of Paxil (paroxetine) and Wellbutrin (bupropion) for unapproved uses. It was the largest fine yet imposed for drug promotion violations.[2]

Whereas the pharma industry's ire is over hefty fines and marketing strictures, physicians focus on the chill that they feel has slowly descended over the free flow of accurate information in the wake of such regulations, backed as they are by the punitive power of the state. For Dr. Donnenfeld, it boils down to a threat to freedom of speech: "That's at the heart of the issue as I understand it. There's a history here where pharmaceutical companies have been sued by the FDA and required to pay enormous fines for representing good information that just wasn't FDA approved, although it was clinically valid." He believes the crackdown and its downstream effects are hurting continuing medical education, and he notes that "cases such as the Allergan suit involving Botox really started the spiral of reducing education."

While Dr. Donnenfeld wants pharmaceutical reps to be free to discuss off-label uses, the threat he sees for continuing medical education is more worrisome: "Right now, most ophthalmologists who give industry-sponsored talks are required to stay to their scripts and can't deviate from what is written in the FDA-approved guide set, and they can't even answer questions when asked by people in the audience. To me, this makes education a farce. Not being able to have a reasonable discussion with people because you're restricted by what you can talk about really violates everything that I feel is important about medicine as well as free speech." As an example, he added, "It's not an unusual circumstance at many industry-sponsored talks to have a compliance officer from the company in the audience, and if you go off label, they'll stop your talk. So, it's certainly very restrictive, and this is a common occurrence, and it limits the ability to educate."

Dr. Donnenfeld continued, "The cost of education is prohibitive today, and for ophthalmologists to receive good, solid information, the partnership between industry and ophthalmology is an important one. While I understand the

concern that we want to make sure the information that's passed along is valid and reasonable, we couldn't accomplish what we do in terms of education without industry support, and the limits that are being placed now really make it very difficult for us to communicate. And I'm talking about every level, about local talks, about residencies, and about national meetings as well. At all these venues, there's been a restriction on education based on governmental control."

Dr. Dell largely agrees: "We have had this absurd situation where, things that everyone knew were true, including manufacturers and physicians, everyone knew a particular pharmaceutical had a particular attribute or benefit, but we could not talk about it in any forum sponsored by pharmaceutical manufacturers. By the same token, the manufacturers could not let their representatives discuss what were arguably standard-of-care uses of their product, simply because the labeling did not describe that use. I think that does a disservice to patients. Ultimately, my yardstick is: is it good for patients? Is it good for physicians? If the answer to both of those is yes, we should be able to discuss those uses freely."

GUIDELINES, POLICIES, AND PRACTICES

To help the relevant players understand the current rules, the FDA periodically issues guidance documents that explain and give examples of allowed and disallowed activity. The documents are freely available on the agency's website, but as with any major bureaucracy, it can take a long time to develop consensus around fundamental policy changes and longer to fully implement those changes. When the issues at hand stir controversy, it can take even longer. As such, some guidance documents regarding marketing off-label uses seem to be getting stale, especially in light of recent court rulings, and updates promised in 2014 have yet to occur.

Of course, ongoing litigation has played a part in the delay, because policy changes cannot be finalized until the legal process has run its course, a circumstance that may be close at hand. In the meantime, the FDA will not discuss potential pending changes, but in correspondence with *CRST*, FDA Press Officer Sarah Petticord sought to explain the agency's current orientation toward off-label promotion: "The FDA issues guidances to share its current thinking on a particular subject, and is just one of the ways the FDA communicates with sponsors regarding the promotion of prescription drugs to ensure that the information contained in a company's promotional materials is not false or misleading. The guidances [sic] … outline the agency's current thinking/recommendations for the dissemination of scientific data about unapproved uses of approved medical products in specific situations: sharing reprints of published research, when directly asked by a physician, and at scientific conferences. The issuance of guidance helps provide clarity to those who manufacture medical products and wish to disseminate scientific information about their products, and provides an opportunity for comment which may help the FDA understand where questions remain."

Essentially, according to Ms. Petticord, the "context of how the information is shared is very important here." Looking forward, she said that "the FDA is working towards a comprehensive guidance that will consolidate the agency's latest thinking on information dissemination regarding unapproved uses of approved medical products."

In addition to the issuance of guidance documents, the agency's Office of Prescription Drug Promotion in the Center for Drug Evaluation and Research administers the FDA Bad Ad program, an outreach initiative designed to educate health care providers about the role they can play in helping the agency make sure that prescription drug advertising and promotion are truthful and not misleading. The program's goal is to help raise awareness among health care providers about misleading prescription drug promotion and provide them with an easy way to report this activity to the agency.

In these pursuits, the FDA still enjoys widespread support among health care providers, who appreciate the agency's help in separating fact from hyperbole with regard to drug and device marketing and promotion. It is a crucial function, according to Dr. Weinstock, whose chief concern is that, "if pharmaceutical companies allow their representatives to use anecdotal reporting of their drugs being used off label, that could be a tremendous danger to the general public, because then you would have a nondoctor giving information to a doctor about something that was anecdotal that they heard. Then, that doctor might go try something on a patient that could be dangerous. There's a big difference between a representative or employee of a pharmaceutical or device company sharing information about off-label use that's anecdotal versus something that has been published in a peer-reviewed journal. That is much more credible and is much more safe and protective for that practitioner and that patient to try. Because it's been vetted, analyzed, and enough of it has been used and studied appropriately that it could be considered safe and effective for that particular patient. So, that is the caveat. It can't be just a carte blanche dissemination of off-label use. There has to be some oversight on what off-label information is shared and make sure that it's credible information that is valid scientifically."

THE COURTS WEIGH IN

In 2009, Orphan Medical's sales representative Alfred Caronia was charged, tried, and found guilty of conspiracy to introduce a misbranded drug into interstate commerce,

in violation of the Federal Drug and Cosmetic Act. In a law enforcement sting, he had been recorded telling his physician customers that Orphan's FDA-approved narcolepsy medication, Xyrem (sodium oxybate), could also be used off label to treat Parkinson disease, multiple sclerosis, fibromyalgia, insomnia, and restless leg syndrome and encouraging its use in unauthorized patient populations. While Orphan Medical and an involved physician pled guilty, Mr. Caronia challenged his conviction with the Second Circuit Court of Appeals. In a largely unanticipated decision in December 2012, it overturned the lower court's ruling, citing that promoting off-label uses truthfully is protected under the First Amendment's freedom of speech clause and is outside the FDA's power to regulate.[3]

Essentially, this was the first substantive legal crack in the previously impenetrable edifice of the FDA's authority over off-label use promotion, and this fact was not lost on the FDA. Instead of appealing the Second Circuit Court's ruling to the Supreme Court of the United States and risking an unappealable loss, the agency chose to narrowly interpret it, mandating that the agency would tolerate limited off-label promotion if marketing materials were approved by the FDA beforehand. The charge of "censorship" was quickly leveled at the FDA and, shortly afterward, was legally challenged by biopharma manufacturer Amarin, headquartered in Dublin, Ireland.[4]

Amarin's drug, a fish-oil derivative called Vascepa (icosapent ethyl), is approved for people with very high triglyceride levels, a condition that has been implicated in cardiovascular disease. Because Amarin hoped to promote Vascepa for patients with less extreme triglyceride levels, it undertook an FDA-approved clinical trial that revealed that the drug does reduce triglycerides in this population as well. As a result of recent questions about the role of triglycerides in heart disease, however, the agency rejected Amarin's application to add this use to the on-label list of indications. Moreover, the FDA told Amarin that, if the company promoted the study results to physicians, it could expect a civil suit or criminal prosecution. Amarin responded by filing its own suit against the FDA in May 2015.[4]

In August 2015, the federal court of New York's Southern District ruled in favor of Amarin and stated that the FDA cannot prevent off-label use promotion as long as it is truthful and not misleading.[5] As in the Caronia case, the FDA chose not to appeal the decision. Instead, with the Court's and Amarin's consent, the agency embarked on a 7-month-long negotiation with Amarin, resulting in an agreement made public on March 8, 2016. In it, Amarin got just about exactly what it wanted. The firm's president and CEO John Thero said in a company statement that Amarin was "pleased to announce this amicable resolution with and among the physician plaintiffs, FDA, and the US government and look[ed] forward to continuing to promote Vascepa in a truthful, nonmisleading, and responsible manner. With more truthful and nonmisleading information readily available to health care professionals about the potential of Vascepa to improve cardiovascular health, this settlement serves the public interest by supporting informed medical decisions for tens of millions of patients with persistent high triglycerides."[6] The implications of the settlement may affect millions of patients, as pharmaceutical companies adjust to this new freedom to promote off-label uses.

GOING FORWARD, TREADING LIGHTLY

In his role as a litigator and consultant with the Washington, DC, law firm Arnold and Porter, Manhu Davar, Esq, has been following the legal cases and the FDA's reactions for years. He spends a signification portion of his professional time helping pharmaceutical companies develop policies and procedures to ensure that they are disseminating truthful and not misleading information. Where they are distributing scientific exchange information, he helps ensure that it falls within the strictures of the FDA regulations governing off-label use. Mr. Davar has also defended companies that are under government investigation and represented them in settlement negotiations in cases involving off-label use. Lately, he has been telling anxious clients to hold steady and wait for the dust to settle, albeit with some optimism toward the likely outcome.

In a recent talk with *CRST*, Mr. Davar described his current advice to clients: "I'm telling people to wait and see, and that's because, if you look at some of the noise around FDA's strategic direction for 2016, it's looking increasingly like they're going to have to address this issue and fix up some of their guidance documents. The only guidance that FDA has put out there on the distribution of reprints has remained in draft form for a number of years, and pharma industry groups, device industry groups, and Congress have all been pushing FDA to give more clarity. Companies realize that—particularly ones that are under investigation—that, to the extent the investigation is premised on simply truthful and nonmisleading speech, that they probably have some good defense arguments. But, the execution risk of going out there and distributing off-label materials without guidance from FDA is still there, and the Department of Justice and FDA are still allowed, if you look at the court's decision in Amarin, to bring cases against companies for distributing false or misleading information. There really isn't guidance right now about how balanced an off-label statement needs to be to keep it from being misleading."

In spite of the current uncertainty, Mr. Davar sees a bright future: "I tell clients that this is a very encouraging

development, and the trend is positive for us in the industry, and I'm hoping that FDA is going to go in the right direction with this, but I'm not telling clients to make any drastic changes to the way they handle off-label information. Where things are now, in my opinion, is that the industry is really encouraged by the Amarin decision."

THE DANCE CONTINUES

In their endless quest for innovative cures and better treatments, bold clinicians will continue to walk the tightrope of off-label use over the chasm of potential disaster. They have to, because history has shown that the rewards are, on balance, worth the risk. Likewise, in their efforts to minimize the harms of careless or misguided clinical experimentation and pharmaceutical marketing fraud, committed employees at the FDA will continue to offer guidance, advice, and the threat of prosecution to help avoid the sort of health care catastrophes that went unchecked when regulation was nearly nonexistent.

With powerhouse drug and device makers seeking profits, doctors trying to protect their freedom to practice effectively, and patients desperate for hope and healing each applying their own forms of pressure to the equation, the stakes remain high. Since the March 2016 agreement between Amarin and FDA, one that left the August 2015 court ruling largely intact, the field seems to have tilted in favor of manufacturers' free speech rights regarding off-label promotion. How the agreement plays out in practice and how the affected players will adjust to the new reality remain to be seen.

For Dr. Dell, there is not much mystery surrounding the outcome: "I am very glad that this ruling and settlement have happened, because it's clear there are many uses of ophthalmic pharmaceuticals that have had their efficacy well established in the medical literature, but the labeling does not describe that usage. So, it's a positive thing, and I'm glad we'll have that change." ■

1. Clark Toni. US FDA to allow Amarin to promote fish oil pill for off-label use. Reuters. March 8, 2016. http://reut.rs/1T1Ijei. Accessed March 2016.
2. Off-label drug prescribing: What does it mean for you? *Consumer Reports*. July 2015. http://bit.ly/1TPeQ9y. Accessed February 2016.
3. Fraizer, Tamara, Ph.D. U.S. v. Caronia: what are the Implications? *Pharmaceutical Compliance Monitor*. March 15, 2013, http://bit.ly/1SLIsRD. Accessed January 2016.
4. A free speech clinic for the FDA. *The Wall Street Journal*. August 14, 2015. http://www.wsj.com/articles/a-free-speech-clinic-for-the-fda-1439593910. Accessed January-February 2016.
5. Burton TM. Amarin wins off-label ruling against FDA. August 7, 2015. *WSJ*. http://on.wsj.com/25XtfWg. Accessed January 2016.
6. Amarin's right to promote Vascepa(R) off-label affirmed under first amendment litigation settlement term. Amarin Corporation, plc. March 8, 2016. http://bit.ly/1TPf3tq. Accessed March 2016.

James Incollingo, MA
- writer, editor, and founder of Texterity, a communication consulting firm
- jim@texterityllc.com; www.linkedin.com/in/jamesjincollingo