Pharmaceutical Manufacturers Alter Sampling Policies

Cataract & Refractive Surgery Today asked several key opinion leaders to weigh in on this pivotal issue.

For fear of potential fines from the FDA, pharmaceutical manufacturers are altering—and in some cases stopping—the sampling of certain antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) to ophthalmic centers and physicians' offices.

Alcon Laboratories, Inc., recently changed its call-and-sampling procedure for Vigamox (moxifloxacin 0.5%), a fluoroquinolone indicated for the treatment of conjunctivitis but commonly used off label in cataract surgery for the prevention of endophthalmitis. Allergan, Inc., has hired a third-party organization to provide samples of Zymaxid (gatifloxacin 0.5%), a fluoroquinolone, and Acuvail (ketorolac 0.45%), an NSAID routinely used off label for the prophylaxis of cystoid macular edema.

Alcon would not comment on why or how it is altering its sampling procedures related to Vigamox, but Allergan attributed its change in policy to an issue of capacity. "It's due to the prioritization of Allergan's eye care sales force against the successful launch of Lumigan 0.01% and Lastacaft, which were recently approved by [the] FDA, and the continued growth of Restasis," Allergan spokeswoman Crystal Muilenburg said in an interview with CRSToday. *"If a physician requests a sample for Zymaxid or Acuvail, instead of the sales force providing them directly, it could be shipped out by a third party."*

All of this leaves drug manufacturers in a difficult position, as they try to build sales of their newer, more expensive drugs without appearing to market products for off-label uses. In addition to sampling, the changes could also affect the way pharmaceutical companies advertise and alter the dialogue between sales representatives and physicians, who often rely on the former for important information about these agents.

Some physicians believe changing marketing practices could also stifle innovation, because there will be less incentive for drug companies to develop new therapeutic agents if they cannot be used for surgical indications. The crackdown on marketing practices also leaves physicians who rely on samples of fluoroquinolones and nonsteroidal anti-inflammatory drugs with some potentially difficult decisions. Many surgeons are now re-evaluating their choice of antibiotic, and some have vowed to move to generic formulations and older generations of drugs. These switches, though, could expose physicians to another unwanted consequence: medical malpractice.

—Stephen Daily, news editor

ERIC D. DONNENFELD, MD

The FDA's recent decision to crack down on the off-label marketing of pharmaceuticals has resulted in fines totaling more than $3 billion being levied on drug makers.[1]

One aspect of the fallout from the FDA's actions is that ophthalmic manufacturers will only sample medications in direct relation to the agent's use in terms of the approved indication. This has prompted both Allergan, Inc., and Alcon Laboratories, Inc., to dramatically reduce their sampling of Zymaxid and Vigamox. Both of these drugs are FDA approved for the treatment of conjunctivitis but not for surgical prophylaxis, for which they are most commonly used.

Allergan attempted to challenge the FDA's crackdown on off-label marketing by suing the agency in federal court. Allergan stated that denying the Botox off-label discussion, which was well documented in the medical literature, was a violation of freedom of speech. As part of its $600 million settlement with the FDA, Allergan agreed to withdraw the lawsuit.[2] Perhaps coincidentally, once Allergan dropped its lawsuit, the FDA suddenly approved several of the company's new products.

The FDA's crackdown is another example of how the agency has exceeded its role of protecting Americans: this has nothing to do with protection. The FDA has made it almost impossible for exciting new drugs to be approved in the United States. Instead, pharmaceutical makers are fleeing abroad, where it is easier, faster, and less expensive to undertake clinical studies. Diquafasol (codevelopers Santen Inc. and Inspire Pharmaceuticals, Inc.), a promising treatment for dry eye, was rejected here but recently approved in Japan. To my knowledge, this is the first time an American ophthalmic pharmaceutical gained approval abroad and not here at home. It has been estimated that the cost of approving a new drug in the United States is over $100 million.[3]

Economically speaking, the United States has been a country that imports significantly more than it exports, resulting in a negative trade balance. Health care has been one of the lone bright spots, but I predict this will not last much longer.

Furthermore, the reduction in sampling will require patients either to pay more for ophthalmic medications or to move toward generic agents. Generic medications, however, are often previous-generation pharmaceuticals that are not prepared in the same way as the premium, brand-name products. These generics can sometimes have deleterious effects on outcomes. Some patients will benefit from the decreased cost but at the expense of an increased risk for a suboptimal outcome.

Most important, I have a real concern about the future of medical care in the United States. A topical antibiotic cannot be marketed for antibiotic prophylaxis for cataract surgery until a study is performed. Performing such a study is impossible because it would be unethical to have a control group not receive an antibiotic. There is simply no reason for ophthalmic pharmaceutical companies to develop new antibiotics. As microbial resistance develops to our current treatment options, we may not have new choices in the very near future because of the decisions being made by today's FDA.

STEPHEN G. SLADE, MD

The halting of surgical samples has important ramifications for surgeons and patients. At my practice, we were using samples for our indigent patients, because the drops cost hundreds of dollars. In some cases, their cost approaches that of the patient's surgery. Our office surveyed the local pharmacies to determine pricing, and even I was amazed at how expensive these medications are. Now, we have few samples, which we save for the patients who really need them. We will also purchase some drops ourselves, which is costly for the practice.

When I prescribe an antibiotic, I should make that decision based on efficacy and less on cost. I do not want to tell patients what is best and then figure out what they—or I—can afford. The patients have certainly noticed what is happening. We have many with insurance plans that do not cover the latest agents, only older antibiotics. It is tough when patients call and ask, "What should I do? My insurance company only covers an older drug."

This is a microcosm of what is happening in health care in general. In this country, we have the ability to provide ultimate care, but we cannot afford to give it to all those who need it. How do we manage this? It is a type of rationing, it is real, and at some point, it will be more prevalent.

I am also disturbed that concerns regarding off-label marketing have led to the halting of samples. I have no problem with a drug representative's telling me what a pharmaceutical agent does, what its off-label uses are, and the experiences of other surgeons. I understand that he or she has a financial interest. *Off label* does not mean that the drug failed or is bad. It only means that it has not been submitted for approval or been approved by the FDA for that specific use. Most drugs and devices, due to simple economics, will never be submitted to FDA trials for every possible use. A huge percentage of what we do as ophthalmologists is off label. This is simply the practice of medicine. Anyone who is performing LASIK retreatments, doing wavefront-guided PRK, or prescribing antibiotics and steroids after surgery is doing so off label. The majority of the treatments in pediatric ophthalmology are off label, because the drugs were approved in adults.

Not allowing us access to this information is censorship. Let physicians, along with their patients, decide what is best for the patient based on all available information and experience. I believe that the people who are ultimately making these decisions do not understand what *off label* really means.

Everything cycles. This pendulum has swung too far. I hope that it starts to swing back.

STEVEN J. DELL, MD

I would like to take this opportunity to publicly address all of the various bacteria that reside in, or contaminate the eyes of, our patients. I hereby formally request that you cease evolving immediately. You see, this will be a necessary step on your part, because we humans will not be developing any new antibiotics for ophthalmic use in the foreseeable future. So, if you could just go ahead and not develop any new antimicrobial resistance capabilities, that would be great. Thank you for your cooperation.

Truly pivotal moments in health care are relatively rare. In the continuum of medical progress, it is difficult to pinpoint a specific event that changed everything. In ophthalmology, however, we have witnessed such an event. Our government, in its wisdom, has laid down the law, and the pharmaceutical industry has snapped to attention. The promotion of the off-label use of FDA-approved medication is radioactive territory and may result in hundreds of millions of dollars in fines as well as criminal charges. Recently, Allergan, Inc. was forced to pay $600 million to settle claims that it promoted Botox for unapproved uses such as headaches.[2]

Although physicians may prescribe drugs for off-label uses when appropriate, we all understand that it is illegal for pharmaceutical companies to promote these uses. A discussion about the propriety of this situation is beyond the scope of this article, but precisely how is "promotion" defined? Corporate sponsorship of educational symposia in which doctors state their own opinions now places these companies in an increasingly uncomfortable position. PowerPoint presentations must be scrubbed of any potentially damaging words, product identifiers, or deviations from approved statements. If clever physicians discover that an approved drug has enormous benefit for the treatment of a different condition, the manufacturer is obligated to pretend that the whole thing never happened. Absurdity.

The way that this is playing out in our little corner of the health care world is that the two largest ophthalmic pharmaceutical companies have concluded that the mere act of providing antibiotic samples and literature to ophthalmologists is a risk they can simply no longer afford to take. The government's message to these companies is clear: most of these antibiotics are used off-label in a postoperative application, so stop promoting them now or face massive fines and criminal charges.

I wonder if the government officials who are responsible for this policy really understand what they have done. Do they imagine that public corporations will spend hundreds of millions of dollars to develop the next antibiotic so they can cheerfully promote it for the odd case of bacterial conjunctivitis? Obviously, they will not. In time, we may find ourselves reminiscing about the days when new antibiotics actually appeared on the market. For every 5,000 to 10,000 compounds that begin initial testing, only one drug reaches the market.[4] The risk-versus-reward proposition, therefore, is already unfavorable for many drugs. If corporations' discussion surrounding drugs is censored to conform to the strict criteria of the FDA's approval, the incentive to invest in new compounds will vanish. This will play out in every sector of health care. Lifesaving advances in cardiology, cancer, or infectious disease will go unfunded, and new uses for old drugs will remain unexplored due to a lack of research funding.

What has happened in the past year or so? Drug development has pretty much come to a halt. The Obama administration has become so alarmed about this situation that it founded a federal research center to help create new medicines.[5] So, the folks who brought us the US Postal Service and the Transportation Security Authority are getting into the drug development business. The newly minted National Center for Advancing Translational Sciences is charged with fostering new drugs, which will then, at some point, be handed off to the private sector. I am sure there are many instances in which governments were able to succeed in commercial enterprises where corporations have failed; I just cannot think of any right now.

WILLIAM B. TRATTLER, MD

I believe the FDA is unreasonable. First, doctors should be instructed on the optimal use of medications for patients—even if the dosing regimen or time frame differs from what the FDA approved. For example, most topical NSAIDs, such as bromfenac and Acuvail (Allergan, Inc.), are labeled to start 1 day prior to cataract surgery, and continue for only 14 days. Others are labeled to start the day after cataract surgery. However, there is research that suggests starting all NSAIDs 3 days preoperatively may have some advantages over the way these medications are labeled. In addition, research has found that extending the NSAID therapy to 1 month postoperatively may help reduce the risk of developing cystoid macular edema. Doctors should be provided with data from studies that look at the optimal use of FDA-approved medications beyond what the label states, and it is my opinion that company representa-

tives should be allowed to share data from studies with physicians, because postapproval study results may help patients.

Another example includes certain drugs that are approved for preventing conjunctivitis. Surgeons have found that they are an important part of the prevention of postoperative infections—and are even considered standard of care. I believe this discussion should be allowed between doctors and the manufacturers.

The FDA should further adjust the way it reviews medications and allow for the approval of those agents used for infection prophylaxis and other conditions based on the available science. It is exceptionally expensive to attempt to conduct a trial that will prove a drug's efficacy regarding the prevention of infection, for example. If a pharmaceutical manufacturer can show that its antibiotic is safe and effective for killing infectious organisms, an allowance show be made for a type of approval that companies may discuss with doctors.

My biggest fear is that there will now be less incentive for companies to produce new therapeutic agents. What company is going to invest $20 million, $50 million, or $100 million in a new antibiotic that can only be approved and promoted for conjunctivitis? If the drug cannot be used or discussed in cataract surgery, where is the incentive for the drug company to develop a novel medication and get it approved?

JOHN F. DOANE, MD

The opportunity to make observations regarding the changing landscape of pharmaceutical sampling, FDA oversight, and companies' being fearful of the off-label use of their products raises several interrelated issues.

About 6 months ago, I was involved in a discussion with other members of the ASCRS Cataract and Refractive Clinical Committees. The point of the discussion was the off-label use of approved devices or pharmaceuticals. To a physician, we came to the same conclusion that about 99% of what we do on a daily basis is off label. Our entire medical and surgical practices are essentially off label. How can this be? Two things come into play. The first key component is that the practice of medicine provides physicians with the opportunity and privilege to use their training, experience, and observational skills to treat diseases and, one hopes, cure patients. The situation is such because of the second component of the reality in which we practice: controlled scientific studies to prove or disprove the innumerable recommendations we make to patients on a daily basis have not or will not likely ever be completed. Possibly to the disdain of health policy wonks, clinical practice pattern-recommendation bureaucrats, controllers of health care remuneration, and plaintiff's attorneys, there simply is not the time or money to validate with a scientific study all that physicians do daily in their practices. To expect unequivocal scientific validation in a profession that is as much art as science will lead to disappointment.

This brings me to the relatively recent decision by pharmaceutical companies to discontinue samples of medications contained in postoperative surgical packs. The apparent reason for the change in samples' availability is that physicians might be using them to care for patients postoperatively, when the medications may not have FDA approval for such use. I think we all agree that it is unacceptable for a company to market a device or medicine for an unapproved use. On the other hand, if a physician via his or her practice of medicine has figured out a useful application for a drug that benefits patients, it seems inherently ethical and moral to prescribe the most effective regimen for the patient.

My best example of this idea is from an occupational and rehabilitation specialist in Kansas City, Missouri. I was referred a patient that needed a combined cataract extraction and corneal endothelial transplantation. Unfortunately, the patient had marked head and neck tremor such that the only way I could have operated was to place her under general anesthesia. I had learned of a colleague's off-label selective use of Botox injections to completely ameliorate tremors or spasticity. Suffice it to say, his ability to resolve my patient's problem and afford her the chance to have sight-correcting surgery without general anesthesia was miraculous from my perspective. Of interest, Allergan, Inc., was fined approximately $600 million for off-label promotions of Botox, and tens of millions of dollars were split between the five whistleblowers that worked for Allergan.[2] I wonder if any patients were hurt by the off-label use of Botox.

My hope is that reason will return to the FDA and the Federal Trade Commission. It seems that the present climate is painting all actors with the same wide brush. On the one hand, these agencies' actions are understandable (the legacy of Vioxx [Merck]), but on the other, it seems that we are witnessing the proverbial baby's being thrown out with the bath water. Medical practice has allowed the discovery of innumerable applications that would otherwise never have been understood, let alone attempted. I hope for a return to a more rational appreciation of this history.

JOHN A. HOVANESIAN, MD

From a macroeconomic perspective, halting free samples of surgical pharmaceuticals may be a positive measure, because surgeons and patients should be choosing a drug based on its merit and relative cost. Previously, surgeons tended to group their prescriptions around one company that was particularly generous with samples, instead of choosing the best drug for each individual situation. Smaller drug makers—even those with superior drugs—would have difficulty competing with the larger companies. In some ways, this situation limits the patient's access to the best drugs. The halting of drug sampling could level the playing field and allow market forces to dominate.

Microeconomically, however, halting sampling has a negative effect. The cost of health care is one of the biggest problems facing this country. One way to address the rising costs is on a case-by-case basis by providing free samples to patients who need them. This is a door that is now theoretically closed, and as a surgeon, I am sorry to see the broad-scale availability of samples go. The worry over liability prevents an act of kindness.

Following the $600 million fine levied last year against Allergan, Inc., for the off-label promotion of Botox, companies are increasingly listening to the advice of their lawyers.[2] The alarming amount of regulation that is dictating the medical industry gets in the way of good patient care. I think we lose a lot more than we gain.

Certainly, there is a trend toward surgeons' prescribing generic formulations more often. If the patient must absorb the cost, surgeons would like to prescribe the lowest-priced medication, which is a sound rationale. In my practice, where about 3,000 cataract cases are performed per year, we made the choice to use generics 1 year ago. Now, however, we are moving back to brand-name medications because we have seen an increase in cystoid macular edema with the use of generic ketorolac, prednisolone acetate, and ofloxacin. Thankfully, we did not see a higher rate of infection, but we certainly saw more inflammatory sequelae when we were using the nonbranded anti-inflammatory agents. We now use Bromday (bromfenac ophthalmic solution, 0.09%; Ista Pharmaceuticals, Inc.), Pred Forte (prednisolone acetate ophthalmic suspension, 1%; Allergan, Inc.), and Vigamox.

As surgeons, we need to do the responsible thing and recognize when generics are appropriate and when they are not, and we must let our patients know as well. At my practice, we are in the process of switching to a brand-name regimen. We give patients a choice and let them know what our recommendation is. We also inform them that, most of the time, patients do fine on generic medications, although that is not always the case. We tell patients, you have cataract surgery twice in your life; is this a chance you want to take? We also encourage our patients to shop around, as there is a wide variety in what pharmacies charge.

What seems to be an accepted truth is that generic agents cost less, and this is not always the case. In Medicare Part D, for example, when patients are in the "donut hole," name-brand medications are discounted 75%. If a patient is prescribed a branded medication that costs $100, he or she will pay $25 and be credited with the full cost of the medication toward his or her deductible. A generic medication that costs $50 is only discounted 6% or 7%. This is an example of how the medication can cost twice as much, but the patient pays less in the donut hole. Patients are better off with branded medications in many cases, and this is not well understood.

RICHARD J. MACKOOL, MD

The major impact of the halting of surgical samples will be an increase in the costs of medical care both for patients and physicians. This action has been made necessary by regulations that prohibit the sampling of drugs that encourages their use for other-than-approved conditions; however, there is no conceivable benefit to anyone from the current situation. Certainly, patients are not protected from improper treatment. They will have to buy medications that they might otherwise have received at no charge, and surgeons who wish to reduce expenses for their patients will be forced to do so at their expense (ie, by purchasing the medications and providing them to their patients).

R. DOYLE STULTING, MD, PHD

The halting of sampling is based on drug manufacturers' fear that they will be found not to be in compliance with regulations, because they are promoting off-label uses of drugs. In this regard, I believe it is inappropriate for the label to control medical care, the sharing of information, or the sampling of drugs. Ophthalmologists typically use drugs and devices off label on a daily basis. Off-label uses are described routinely in textbooks, and we would probably all be susceptible to malpractice suits if we did not prescribe off label.

There are many reasons why a particular indication for which a drug or device is effective may not be men-

tioned on the label. The manufacturer of that drug or device may have decided not to include patients with this indication in clinical trials because of cost or other issues. For example, almost all topical ocular antibiotics are evaluated and labeled for the treatment of conjunctivitis, because such patients are easy to recruit, tend to present a homogenous population, and provide an experimental population with which the FDA is familiar. Topical antibiotics are used routinely, however, for the treatment of corneal ulcers—a practice that is taught in medical school, is recommended in textbooks, and is the standard of care. If a patient presents with a corneal ulcer caused by an organism with unique susceptibility to an antibiotic that is not labeled for use with corneal ulcers, the practitioner had better prescribe that antibiotic, in spite of the fact that it is an off-label use.

A drug or device may be used off label because data become available to support its safety and efficacy after clinical trials were completed. Contraindications to the use of drugs or devices may also become apparent only after approval, so the converse of the typical "off-label argument" may be true: practitioners may sometimes not be providing optimal care if they follow the label.

Sampling provides practitioners with an opportunity to gain experience with new drugs. It also meets other needs for some patients, like providing drugs that are urgently needed for immediate treatment after normal business hours or for the treatment of indigent patients.

It is sad that the government has decided to interfere with medical practice by blocking communication between manufacturers and physicians. The government has implied and expressed condemnation of off-label use and has taken steps that have caused manufacturers to discontinue sampling and stop sharing legitimate scientific information about off-label use. This interference will have a significantly detrimental effect on the services that physicians are able to provide, on their scientific knowledge, and on the health of US citizens. ■

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