FDA Revisits Rules on Drug and Device Communication

Will the Agency Relax Existing Industry-Opposed Restrictions?

Stephen Barlas

Even before President Donald Trump appointed a new commissioner at the Food and Drug Administration (FDA), that sometimes-slaghish agency issued early statements that seem to indicate its officials are aware of the deregulatory winds now being generated by the White House and Congress. In early January, the agency released two guidance documents and a question-and-answer memorandum that, if they didn’t formally reverse current policies restricting drug and device manufacturer communications with various audiences, at least sought to show agency leaders’ flexibility and openness to industry complaints. One draft guidance dealt with health care economic information (HCEI)1 and the other with product labels;2 the question and answer (Q&A) memorandum covered First Amendment issues.3

The draft guidance on HCEI clarifies and expands the types of information companies can send P&T and formulary committees under Section 114 of the Food and Drug Administration Modernization Act (FDAMA). The FDA was responding in part to a provision in the 21st Century Cures Act that Congress passed in December. But the appearance of the draft guidance one month later—which would otherwise have been a world-record time for FDA action—clearly indicated that the agency had the draft guidance in the works long before Congress passed the bill.

Jennifer Graff, Vice President of Comparative Effectiveness Research (CER) at the National Pharmaceutical Council (NPC), says, “The draft guidance on HCEI definitely shines a lot more light on the kinds of data companies can provide and who can receive the data.”

Drug and device manufacturers have criticized the FDA’s off-label promotion restrictions over the past two decades. Those policies have stemmed from another FDAMA section, 401. The Washington Legal Foundation (WLF) has litigated several cases in this area. WLF Chief Counsel Richard Samp held a two-day meeting to explore potential changes in its drug and device companies, says: “I and others were pleasantly surprised how engaged the agency was. It was clear from questions from the FDA panel that officials at the agency recognize value in off-label communications and additional clarity and flexibility is needed.”

Free speech issues have been at the root of complaints about how the FDA has implemented both Section 401 and Section 114. Section 401 has been the more controversial of the two, with the Justice Department winning big judgments against drug companies and, in the reverse situation, drug companies suing the FDA and winning after receiving warning letters.

It may be that the most significant FDA action in January was publication of the draft guidance entitled Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers.1 Health insurers have been clamoring for new flexibility on receiving (and drug companies on providing) HCEI so they can structure more affordable value-based contracts with drug manufacturers. That clamor led to Congressional passage of an amendment to Section 114 in the 21st Century Cures Act. In terms of requirements that companies would have to meet regarding the quality of any data they provide, the draft guidance essentially reaffirms the existing competent and reliable standard but provides examples of what this would include. The guidance gives a shout-out in a footnote to the tools published by the CER Collaborative, which is composed of the NPC, the Academy of Managed Care Pharmacy (AMCP), and the International Society for Pharmacoeconomics and Outcomes Research.

While the FDA probably received a political nudge from the 21st Century Cures bill, it had already been thinking about changes it wanted to make in restrictions to on-label and off-label communications. In November 2016, the FDA held a two-day meeting to explore potential changes in its communications policies for drug and device manufacturers. Kellie Combs, an attorney at Ropes & Gray who represents the Medical Information Working Group (MIWG) made up of drug and device companies, says: “I and others were pleasantly surprised how engaged the agency was. It was clear from questions from the FDA panel that officials at the agency recognize value in off-label communications and additional clarity and flexibility is needed.”

The History

Over the past two decades, it has been off-label communications, not HCEI, that has been the hottest-button communications issue for drug companies, which want greater flexibility to promote unapproved uses of their products to physicians and sometimes to insurers. The proposed new guidance outlines what medical texts and peer-reviewed studies on off-label uses of drugs and medical devices can be provided to insurers and medical professionals. It prohibits texts that are: 1) published specifically at the request of a drug or device manufacturer; or 2) primarily distributed by a drug or device manufacturer, as opposed to independent distribution channels where textbooks are sold. It also imposes disclaimer requirements on

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manufacturers, such as a requirement that the approved labeling be included “for each of the manufacturer’s products that is included in the distributed chapter(s).” Section 401 lapsed due to a sunset provision in 2006, and the FDA put out a draft guidance document in 2009 laying out the kind of off-label promotions it would allow without branding them a false and misleading marketing claim, authority the FDA has under the Food, Drug, and Cosmetics Act. The agency refined that draft guidance in 2014. The FDA has never conducted a rulemaking on off-label promotion, which would put a bright line—and a legally enforceable one—in federal law. But the agency has tended to argue that off-label information has to be “scientifically valid” in addition to not being false and misleading. That “scientifically valid” requirement is generally translated into the need to have well-designed, credible, randomized clinical trials to back up any off-label communication.

There has been little if any legal action around Section 114, which drug companies have been hesitant to use because the FDA has never issued guidance. It defines HCEI as an analysis that identifies, measures, or compares the economic consequences of the use of the drug to the use of another drug, another health care intervention, or no intervention. The information will not be considered false or misleading if it is based on “competent and reliable scientific evidence.”

Drug and device manufacturers have long criticized the FDA’s enforcement policy on Section 401 as being anti-First Amendment, and the WLF has carried the ball in numerous court cases. The drug industry has received substantial fines in recent years for illegally promoting medications for off-label uses, including the $3 billion paid by GlaxoSmithKline in 2012 for, among other things, the off-label promotion of its antidepressant drugs paroxetine (Paxil) and bupropion (Wellbutrin), Johnson & Johnson and its subsidiaries paid more than $2.2 billion in 2013 to resolve criminal and civil liability arising from allegations relating to the prescription drugs risperidone (Risperdal), paliperidone (Invega), and nesiritide (Natrecor), including promotion for uses not approved as safe and effective by the FDA and payment of kickbacks to physicians and to the nation’s largest long-term care pharmacy provider. In 2014, Pfizer agreed to pay $325 million to wrap up claims that its Parke-Davis unit touted the epilepsy drug gabapentin (Neurontin) for uses not approved by the FDA.

But in 2015 Amarin won a federal court case against the FDA that vindicated the company’s actions telling physicians about studies supporting the use of the fish-oil–derived cardio drug Vascepa (icosapent ethyl) for uses not approved by the FDA. As long as the statements Amarin made were “truthful,” the court said, they did not constitute misbranding. The FDA approved the drug in 2012 for people with extremely high levels of triglycerides. It rejected a second indication for people with slightly lower levels of triglycerides. Amarin sued and in 2015 a U.S. District Court in New York ruled Amarin could promote Vascepa off-label for the second use because its off-label claims were “truthful.”

Another federal court sided with Pacira Pharmaceuticals, Inc., which the FDA said had misbranded its nonopioid painkiller Exparel (bupivacaine liposome injectable suspension). As part of a December 2015 settlement, labeling changes were made that reaffirmed the off-label, or unapproved, uses of Exparel, along with a rescission letter from the FDA formally retracting its September 2014 warning letter.

Besides criticism from drug and device manufacturers and insurers, the FDA’s off-label policy has ticked off prominent congressional Republicans. The two top Republicans on the House Energy and Commerce Committee, which has oversight of the FDA, filed on last May. Representatives Fred Upton (R-Michigan), chairman of the committee, and Joseph Pitts (R-Pennsylvania), chairman of the health subcommittee, wrote to Sylvia Burwell, then Secretary of the Department of Health and Human Services, saying they are “increasingly perplexed by the agency’s unwillingness or inability to publicly clarify its current thinking” on off-label communications. The two Republicans cited recent court decisions where the FDA’s “misbranding” rationale for taking enforcement action did not hold water.

In opening the meeting last November, former FDA Commissioner Robert Califf presented an “on the one hand, on the other hand” reasoning for the FDA’s re-examination of its current policy. He cited a Canadian study that showed unapproved uses of approved drugs leading to a substantial increase in adverse events. But he went on to ask for evidence on the extent to which health care providers currently face challenges in accessing relevant information, and whether information that drug manufacturers have but are prohibited from providing could contribute relevant, scientifically sound, and nonmisleading information.

New Developments Push Liberalization Agenda

In their drive to expand communications, drug and device companies have two separate audiences: physicians and other health professionals on one hand, insurance companies and other payors on the other. In the first instance, the issue is off-label communications. With regard to promotion to physicians (although health insurers are included as a potential audience under Section 401), drug companies are making the argument that patients are the ones who suffer as a result of the FDA’s restrictive First Amendment-First policy. Take Pfizer, for example. In one instance, it supplied physicians, through its pharmaceutical representatives, with dosing information on an oncology medicine that has a specific dosing regimen on its label. But certain patients have tolerance problems at those dosing levels. About two years ago, several international oncology journals published results from multiple retrospective studies, in which patients who experience tolerance issues with the labeled dosing regimen were switched to a specific alternative dosing regimen. However, because the information came from retrospective studies, it did not meet the traditional substantial evidence standard required by the agency. “We had no doubt that communicating this information was the right thing to do for patients, but the agency’s existing policies don’t clearly permit a company to communicate this type of data proactively,” states Andrew Koenig, a rheumatologist and a member of the Inflammation and Immunology Medical Group at Pfizer. “While we chose to move forward on that occasion, there are many other instances in which Pfizer has either long delayed allowing or not allowed our representatives to communicate data that does meet the substantial evidence standard out of concern of regulatory enforcement actions.”
But insurance companies are really driving the debate on Section 114-type information. The introduction of specialty drugs with six-figure annual costs in the past few years has been a driver of interest in the receipt of wider kinds of information by insurers. “We are seeing more and more pharmaceutical products come to market with five- and even six-figure price tags, some with patient populations numbering in the millions, not the thousands,” says Douglas Stoss, Vice President of Federal Affairs at Humana. “As a result, it is more important than ever that payers be able to talk to manufacturers about on-label and off-label indications, as well as pricing and projected utilization.”

Cartier Esham, Executive Vice President for Emerging Companies at the Biotechnology Innovation Organization, offers this explanation:

The current FDAMA 114 standard on post-launch communications to formulary committees or other similar entities requires that such information directly relates to an approved indication. This standard is open to interpretation and can be problematic. For example, economic research about disease costs and outcomes goes beyond the narrow scope of a specific indication, yet it is relevant in the context of an insurer’s decision to cover a therapy, and what, if any, utilization management restrictions to place on that coverage.

What Kind of Information

With regard to both off-label and on-label information, drug and device manufacturers want to be able to supply data beyond what is developed through clinical trials. The ability to produce real-world evidence (RWE) instead of data from well-designed clinical trials would incentivize drug companies, so the argument goes, to apply to the FDA for new indications instead of promoting a drug off-label, for example. RWE, in the context of its use in applying for new indications, refers to data on safety and efficacy assembled from observational studies or based on medical claims data and the like. Aaron Kesselheim, MD, JD, MPH, Program on Regulation, Therapeutics, and Law (PORTAL) at Harvard Medical School, says, “One way would be to bypass the traditional clinical trial for off-label indications in favor of real-world evidence that could be provided by PCORNet studies or other large pragmatic trials.” PCORNet, the National Patient-Centered Clinical Research Network, assembles RWE evidence outside clinical trials by plugging into the health care data volunteered by insurance companies in the form of claims data and by individuals who offer their access to their electronic health records.

With regard to RWE in the context of HCEI, the FDA does appear to clarify some issues in the new draft guidance. There the agency reiterates what has been its current standard for assuring the scientific legitimacy of any HCEI—i.e., “competent and reliable scientific evidence”—but defines for the first time what this would require by noting it will consider the merits of existing current good research practices for substantiation developed by authoritative bodies (e.g., International Society for Pharmacoeconomic and Outcomes Research [ISPOR], Patient-Centered Outcomes Research Institute).

The ISPOR has joined with the NPC and the AMCP to create checklists and online tools to help population decision-makers evaluate whether evidence is reliable and credible. These are offered through the CER Collaborative. These tools are available to the public, including P&T committees, and could help drug and device companies demonstrate that their HCEI meets the FDA standard for communication.

The NPC’s Graff notes that the draft guidance issued in January shows new flexibility. It provides a number of illustrative cases that allow companies to go beyond information directly related to the drug’s label. So, for example, if a label discusses the results of a 12-week clinical trial, HCEI could look to longer periods and talk about, for example, data showing whether patients stick to their treatment regimens at 24 weeks. The draft also lists what kind of HCEI can be provided on investigational new drugs, something health insurers have been pressing for. That information must be “unbiased, factual, accurate, and nonmisleading.”

Those are some of the same terms the FDA has used to judge the legality of off-label promotion. The Q&A memorandum the agency issued in January doesn’t appear to provide any new flexibility, although the agency sounds as if it might listen to reasonable arguments going forward. As Samp explains:

The Memorandum does not suggest that FDA is seriously contemplating a revision in its speech-restriction policies. The FDA continues to insist that truthful manufacturer speech regarding off-label uses can and should be used as evidence of an intent to market a product for an unapproved new use, despite the rejection of that approach by the [U.S. Court of Appeals for the] Second Circuit and other courts. FDA also fails to acknowledge that the context of truthful off-label communications plays an important role in determining whether the First Amendment bars FDA from sanctioning the speakers.

Conflicting Voices on Off-Label Policy

While the FDA with its new guidance probably provides some assurance for companies wanting to give HCEI to insurers, it still has not gone beyond the 2014 revised draft guidance on off-label communications to physicians. The Pharmaceutical Research and Manufacturers of America would like to see the creation of a safe harbor to protect communication to health care professionals regarding medically accepted unapproved uses of FDA-approved medicines including, in particular, uses recognized by national medical associations and compendia services. The information would have to be based on scientifically and statistically sound methodologies and could include pharmacoeconomic data, post hoc analyses of clinical trial results, subpopulation analyses, and observational data or real-world evidence. But it is not clear how far off the current scientifically valid standard the industry wants the FDA to move.

While supporters of FDA liberalization argue that standards such as scientifically valid backed by well-controlled clinical trials are anti-First Amendment, opponents of reform take the opposite tack. They say that clinical trials, even if peer-reviewed, are no guarantee of scientific worth. Vikas Saini, MD, President of The Lown Institute, says, “Publication in the peer-reviewed literature, the most plausible location for meaningful off-label information, is not necessarily valid scientific information. The peer-reviewed literature is woefully inadequate.”

Opponents argue that the industry simply wants to increase sales of products that have not been proven safe and effective

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by promoting off label uses. Michael Carome, Director of the Public Citizen’s Health Research Group, says a wide range of problems commonly undermine the integrity of clinical trial data reported in peer-reviewed scientific and medical journal articles. He thinks the FDA’s existing January 2009 guidance for industry on good reprint practices weakens the U.S. regulatory process for ensuring that prescription drugs and medical devices are safe and effective for their intended uses, and poses a substantial risk of harm to patients. “Much tighter limits on such communications are essential to protect patients and public health,” he states.

Sidney Wolfe, Founder and Senior Adviser of Public Citizen’s Health Research Group, is concerned that off-label use has higher rates of adverse reactions than on-label use. To support his argument, he points to an article in *JAMA Internal Medicine* published online on November 2, 2015. The study was based on prescriptions dispensed over a four-year period in Quebec, Canada, to 46,000 patients.4

The degree to which the FDA liberalizes its on- and off-label communications policies will depend in part on the identity of a new commissioner and the extent to which any proposed changes run into resistance from Republicans on Capitol Hill who may be susceptible to complaints from some patient advocacy groups that drug safety concerns are being overridden. They would have the support of Democrats, who on their own will be mostly powerless for at least the next two years until the next congressional elections, and maybe for the next four years, depending on the outcome of those elections.

REFERENCES


