For years, the Food and Drug Administration has recognized that there is a prevalence of off-label use of drugs approved by FDA for specific indications, there is clinical relevance and value from such off-label use, and there is a large amount of information about both on- and off-label uses of such drugs available even with a limited ability by manufacturers to disseminate this information. This recognition requires a balancing by FDA between enforcing the Food, Drug, and Cosmetic Act’s regulations prohibiting promotion of off-label use and permitting dissemination of off-label information to healthcare professionals for use in treating their patients. Key to this balancing act is FDA’s position that any off-label discussions by manufacturers constitutes “misbranding” and are in violation of FDCA. Recent success by manufacturers establishing that disclosure of truthful and non-misleading information about off-label use of their products is protected commercial speech has thrown the FDA’s balance out of whack. While currently limited in scope, such challenges may change the FDA’s enforcement actions to focus more on false and misleading content in such off-label discussions and less on a presumption of “misbranding” based solely on the fact of off-label discussions.
I. FDCA AND MARKETING OF DRUGS

The FDCA and its amendments create the statutory requirement for drugs to be approved for safety and effectiveness for their intended uses before being introduced into commerce. The FDA has long maintained that manufacturers must market and promote products consistent with the FDA-approved labeling, and therefore off-label use means “misbranded” under the FDCA.

In addition to FDA’s own enforcement activities, the Department of Justice, in conjunction with the FDA, have in recent years actively pursued enforcement of misbranding provisions against drug manufacturers by claiming that off-label promotion by manufacturers has generated increased requests for reimbursement of healthcare claims in violation of the False Claims Act. With the punitive consequence of exclusion from participation in federal healthcare programs, these misbranding claims have resulted in numerous significant settlements with manufacturers, such as Pfizer in 2009 ($2.3 billion), Abbott Laboratories, Inc. in 2012 ($1.5 billion), and GlaxoSmithKline LLC in 2012 ($3 billion), among others.

II. FDA GUIDANCE ON DISSEMINATION OF OFF-LABEL INFORMATION

The FDA recognizes that off-label uses by healthcare professionals may be important to support public health regardless of their approved indications. In fact, off-label use may be supported in published medical literature and journals and may even constitute the medically recognized standard of care. In order to restrict the expansion of off-label use, FDA issued guidance permitting some limited dissemination of materials related to off-label uses.

A 2009 FDA guidance document describes the process permitting manufacturers to disseminate medical or scientific publications about off-label uses of their products. That draft guidance was replaced in February 2014 to specify revised requirements and limitations on when such published materials can be distributed. To avoid misbranding, such materials must: be created by independent experts; contain scientifically sound evaluations; not be false or misleading; not be written by or influenced by a manufacturer; be provided in unabridged form; be distributed separately from promotional information or material; be distributed with FDA-approved labeling; be distributed with a bibliography of publications describing the clinical studies about the off-label use; and be distributed with a prominent statement that the use discussed has not been approved by FDA, including any known risks or safety concerns related to the off-label use.

In addition to the proactive dissemination of content to physicians and healthcare entities described above, FDA issued a 2011 draft guidance allowing the reactive dissemination of information in response to unsolicited requests for off-label information. Pursuant to such draft guidance, manufacturers may respond to unsolicited requests for information about off-label uses of their products. The responses must be truthful, balanced, and non-misleading, non-promotional, scientific or medical information; limited to the specific request; delivered to the specific individual who requested the information; delivered by medical or scientific personnel independent from the sales and marketing departments; and include any FDA-required labeling.

The FDA has long maintained that manufacturers must market and promote products consistent with the FDA-approved labeling, and therefore off-label use means “misbranded” under the FDCA.
III. RECENT CHALLENGES ON FIRST AMENDMENT GROUNDS

While the existing FDA guidance provides a mechanism for sharing off-label information, the restrictions in such guidance have frustrated the ability to make the information available in a timely and concise manner. Some manufacturers, emboldened by recent court rulings, have pursued constitutional challenges to these restrictions based on first amendment protected speech grounds. In a December 2012 decision, the Second Circuit, in United States v. Caronia, vacated the conviction of a pharmaceutical sales representative for conspiring to promote a drug for off-label use. Caronia argued that his sales pitch, using truthful and non-misleading information, is protected speech under the First Amendment. The court agreed, and because there is no specific prohibition against off-label promotion, such speech may not be the basis of a prosecution for misbranding.\(^\text{15}\)

On May 7, 2015, Amarin Pharmaceuticals went on offense, filing a complaint to permit it to share truthful and non-misleading speech promoting the lawful, off-label use of an FDA-approved drug.\(^\text{16}\)

Amarin responded by filing a complaint seeking declaratory and injunctive relief that FDA’s restrictions on Pacira’s truthful and non-misleading speech harmed Pacira’s commercial interests and ability to advance public health.\(^\text{17}\) In October 2011, the FDA approved Exparel® for post-surgical pain management based on a demonstration of safety and effectiveness in two clinical trials for soft tissue and hard tissue applications. In September 2014, FDA issued a warning letter to Pacira demanding that it stop providing instructions that imply Exparel is approved for use in procedures other than the two specific applications from the clinical trials. Pacira responded to FDA, outlining its disagreement that the materials violated the FDCA. In July 2015, FDA issued a closing letter regarding Pacira’s warning letter, concluding that Pacira’s speech was violative of the FDCA which led to the filing of the complaint.

The parties then entered a settlement agreement on December 14, 2015, resulting in a mutual release of claims, a withdrawal of the warning letter with an FDA letter of explanation, a revision of the product labeling and instructions, and a confirmation by FDA that the drug was approved for broad use across various applications, not just for the two procedures originally tested. While the settlement did not respond to the rights of Pacira to discuss off-label uses, it did expressly preserve Pacira’s ability to assert constitutional rights related to its Exparel marketing efforts.

In March 2016, Amarin and FDA settled their dispute, and FDA acknowledged (by accepting the court’s determination) that Amarin’s proposed statements were truthful and non-misleading. Amarin agreed to assure its communications remained truthful, and FDA agreed to preview up to two proposed communications by Amarin and to provide Amarin with any concerns FDA may have with the communications. The parties agreed to an established dispute resolution process prior to requesting judicial resolution.

While the existing FDA guidance provides a mechanism for sharing off-label information, the restrictions in such guidance have frustrated the ability to make the information available in a timely and concise manner.
A manufacturer should have a process to vet and script in advance the statements it intends to make about a drug’s off-label use to assure that its communications remain truthful and non-misleading.

First, as observed by the court in Amarin and agreed to by Amarin in its settlement, a manufacturer should have a process to vet and script in advance the statements it intends to make about a drug’s off-label use to assure that its communications remain truthful and non-misleading.

These decisions will not protect manufacturers from speech that is false or misleading. Also, manufacturers must remain diligent in reviewing content to be disseminated and ensure that appropriate training is provided to the representatives engaged in discussions about their products, whether sales, marketing or other specialties, to make sure they do not “misbrand” their products. This is emphasized by the FDA’s public statements since Coriorn that it does not view these decisions as significantly affecting its enforcement of the misbranding provisions of the FCPA, even though it will likely cause FDA to be more prudent in its enforcement activities.

Second, the decisions do not protect manufacturers if the government uses the off-label speech as evidence in cases under the False Claims Act, although it will make it more difficult to prove that the lawful, truthful and non-misleading speech caused the submission of a non-reimbursable claim.

Third, while the Coriorn decision applies to government prosecution of manufacturers generally in the promotion of lawful, off-label use of an approved drug, it is worth noting that FDA elected not to seek a petition for certiorari, thus leaving the decision somewhat limited. While the settlement in Pacira did serve to preserve Pacira’s first amendment rights, the resolution of the matter did not turn as much on the constitutional rights issue as it did on permitting Pacira to rely upon the broad indication issued by FDA in its original approval and preventing the FDA from seeking to limit the approved indications of products without following its own regulations and due process.

These decisions provide some additional latitude to manufacturers to discuss truthful and non-misleading information about their products, but they should not be viewed as providing broad protection to promote off-label uses as constitutionally protected free speech. Manufacturers remain obligated to maintain a review process for any information or material communicated to their customers.