Generally speaking, FDA-approved drugs (and devices) come with package inserts and marketing information that specify one or more approved “indications,” that is, the illnesses or medical conditions for which the FDA determined that the drug (or device) has been shown to be both safe and effective. In addition to these “indicated” uses, the Federal Food, Drug and Cosmetic Act (FDCA) and associated regulations generally permit physicians to prescribe approved drugs for other than their specified indications, a practice commonly referred to as “off-label” use. Importantly, however, pharmaceutical manufacturers are not allowed to promote a drug for any other purpose than the indicated use (such as marketing an “off label” use) without formal FDA approval.

The FDA’s longstanding position is that a manufacturer that promotes a drug for an unapproved use violates the FDCA in two ways. First, the FDCA prohibits companies from introducing unapproved “new drugs” into interstate commerce, and the FDA regards off-label promotion as an unapproved “new drug” for that particular use. Before a “new drug” can be marketed in the U.S., the FDA must approve it.

Second, the FDCA prohibits companies from introducing a “misbranded” drug into interstate commerce, and the FDA contends that off-label promotion “misbrands” a product. A drug is “misbranded” under the FDCA if, among other things, its labeling (i) is false or misleading, (ii) does not contain adequate warnings, or (iii) does not contain “adequate directions for use.” According to the FDA, a drug’s approved labeling cannot contain “adequate directions for use” with respect to any off-label use, because the manufacturer cannot write “adequate

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directions” for medical uses of the drug that were not approved by FDA, and were not thereby proven to be safe and effective.

Off-label promotion can create a host of legal liabilities, both civil and criminal. In a continuing shift of enforcement strategy, the U.S. Department of Justice (DOJ) and Qui Tam relators have successfully used off-label use allegations against pharmaceutical, biotechnology, and medical device manufacturers in bringing civil enforcement actions under the Federal False Claims Act. These actions have resulted in a series of large monetary settlements. Additionally, various U.S. attorneys’ offices around the country have brought companion and stand-alone criminal prosecutions against the life science industry through the criminal provisions of the FDCA and the healthcare Anti-Kickback Statute. Additionally, the Lanham Act, product liability claims, and state unfair trade practice laws, add to the list of possible causes of action against companies.

With respect to the criminal aspect of off-label marketing, such promotion can constitute health care fraud under the theory that public health care programs like Medicare and Medicaid should not and do not reimburse for uses of products that are not specifically approved by the FDA. Indeed, parties have been prosecuted for health care fraud (and conspiracy to commit health care fraud) for submitting reimbursement claims to Medicare and Medicaid for off-label prescriptions under the theory that this conduct constitutes a scheme to obtain money from the government by false and fraudulent pretenses, which may support charges under the criminal False Claims Act, as well as the mail and wire fraud statutes.

Efforts to promote products for off-label uses have also given rise to criminal liability under the federal Anti-Kickback Statute, which prohibits anyone from knowingly and willfully offering, paying, soliciting, or receiving any remuneration to induce the purchasing, ordering, or
recommending of any good or service reimbursable by any federal health care program. Companies have been charged with violating this statute as a result of making direct and indirect payments to physicians who agree or offer to agree to write prescriptions for the off-label use. These payments can come in the form of cash, lavish vacations, staffing assistance and free product, among others. Finally, companies under investigation for off-label promotion have been indicted for making false statements to the government and obstructing justice during the course of investigations.

There are certain circumstances, however, where a manufacturer’s off-label promotion is viewed by the FDA as acceptable, such as the distribution of medical journals discussing the pros and cons of certain off-label uses. To clarify its viewpoint on this issue, the FDA released a guidance document to the industry entitled, “Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices.” The guidance provides drug and device manufacturers with the agency’s views on the distribution of medical journal articles and scientific or medical reference publications that discuss new unapproved uses for FDA-approved drugs and FDA-approved or cleared medical devices to healthcare professionals and healthcare entities.

The guidance identifies permissible conditions under which FDA would not consider the distribution of certain materials to be evidence of off-label promotion. Under the Guidance, disseminated information must:

- Be published by an organization that has an editorial board that uses experts with demonstrated expertise in the subject of an article and who objectively select,
reject, or provide comments about proposed articles. The organization also must adhere to a published conflict of interest disclosure policy;

- Be reviewed in accordance with peer-review procedures;
- Not be presented in an industry-funded special supplement or publication;
- Comprise truthful and non-misleading content that is reflective of adequate and well controlled clinical investigations; be presented as an unabridged reprint or copy and not marked, highlighted, summarized, or characterized in any way;
- Include a disclosure statement regarding the unapproved nature of the use described, relevant financial interests, and any significant risks or safety concerns known to the manufacturer that are not discussed in the publication;
- Be disseminated with approved labeling and a comprehensive bibliography of publications related to the off-label use;
- Be disseminated with a representative publication researching contrary or different conclusions regarding the off-label use (if any);
- Be provided separately from information that is promotional in nature; and
- Be limited in distribution to healthcare practitioners and entities such as pharmacy benefits managers, health insurers, or federal and state governmental agencies—but not consumers.

In response to criticism that the distribution of off-label reprints undermines the regulatory approval process and potentially adversely affects patient care, the guidance expressly encourages manufacturers to seek formal approval/clearance for new indications and intended uses of medical products. Additionally, the FDA has broadened its description of potential legal violations, and stated that its authority to determine whether certain activities constitute unlawful
promotion of unapproved products, or causes a product to be misbranded or adulterated remains unchanged. There is no requirement, however, that companies submit off-label materials to the FDA; nor is a manufacturer obligated to file or promise to file a supplemental application for the off-label use of described or disseminated materials, although both are encouraged. Importantly, the FDA continues to perceive “important public health and policy justification” for manufacturer dissemination of off-label, peer-reviewed, scientific journal articles, and reference publications. Thus, there exists some tension (and ambiguity) between these two competing points of view, and it remains to be seen in which direction (enforcement versus acquiescence) the pendulum will swing in the future.