FDA Issues Draft Guidance Relating to Distribution of New Risk Information for Approved Drugs and Biologics and Grants Two Citizen Petitions Regarding Manufacturer Speech

On June 6, 2014, the Food and Drug Administration ("FDA") issued two documents that reflect the agency's ongoing effort to clarify its regulatory approach regarding manufacturer communication of scientific and medical information to health care professionals ("HCPs"). The two documents are (1) a draft guidance document entitled "*Guidance for Industry: Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices*"; and (2) a response granting the two pending citizen petitions[1] filed by members of the Medical Information Working Group ("MIWG"), an ad hoc coalition of drug and device manufacturers to which Ropes & Gray LLP serves as one of the outside counsel. This alert summarizes the key aspects of each document.

Scope of the Draft Guidance

The draft guidance creates a very narrow safe harbor under which a manufacturer of a prescription drug or biological product may distribute risk information that may be inconsistent with the risk information contained in the product's approved labeling. The underlying assumption is that FDA has acknowledged that it is not necessarily false or misleading to disseminate information that does not meet the "substantial evidence" standard established in the agency's regulations.

Under the terms of the draft guidance, the safe harbor applies to the distribution of peer-reviewed publications containing "new risk information" about approved drug and biological products to HCPs. The draft guidance defines "new risk information" as "information that becomes available after a drug is marketed that rebuts or mitigates information about a risk already identified in the approved labeling or otherwise refines risk information in the approved labeling in a way that does not indicate greater seriousness of the risk."[2]

The draft guidance expressly excludes information about a newly identified risk or new information that indicates a risk identified in approved labeling is more serious than reflected in the labeling from the definition of "new risk information."[3]

Distribution Principles for New Risk Information

The draft guidance recognizes that there are limits on the ability of premarket risk assessment to fully characterize a drug's safety profile and that it is important to provide a mechanism for distributing useful new risk information to HCPs in a timely manner. FDA, therefore, "does not intend to object" to distribution of

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[1] *See* July 2011 Citizen Petition FDA-2011-P-0512; September 2013 Citizen Petition FDA-2013-P- 1079.

[2] The draft guidance provides three examples of new risk information: (1) data indicating that the severity or rate of occurrence of an event is lower than described in approved labeling; (2) data that call into question a causal relationship between a drug and an event in the approved labeling; and (3) data that supplement risk information for a general population with risk information concerning a subpopulation of interest.

[3] FDA also recognized "differences in the purpose, nature, and reliability of the evidence" used to show effectiveness versus the evidence that is the basis for a product's risk assessment. The draft guidance does not apply to evidence related to effectiveness.

medical and scientific publications containing new risk information that "rebuts, mitigates, or refines risk information in the approved labeling" if the following criteria are satisfied:

Data Source:

- The study or analysis should meet accepted design and other methodologic standards for the type of study or analysis and be "sufficiently well-designed and informative to merit consideration" of the risk discussed.
- The study or analysis should be "at least as persuasive as" the data that underlie the existing risk assessment of causality, severity, and/or incidence of the adverse reaction as reflected in approved labeling, such as a new controlled trial designed to estimate the relative risk of the event or a rigorous meta-analysis of all relevant data from new and existing controlled trials.
- The conclusions of the study or analysis should give "appropriate weight and consideration to, and should be a fair characterization of, all relevant information in the safety database," including contrary or otherwise inconsistent findings.
- The study or analysis should be published in an independent, peer-reviewed journal.

Distribution:

- The reprint should be accompanied by a cover sheet that "clearly and prominently" discloses: (1) the study design, critical findings, and significant limitations that may limit the persuasiveness or scope of findings; (2) that the information is not consistent with certain risk information in the approved labeling; (3) that FDA has not reviewed the data; and (4) any financial interests or affiliations between the study authors and the firm.
- The reprint should be accompanied by the approved labeling.
- The reprint should be distributed separately from any promotional material.
- Any statements made by a representative of the firm to a recipient concerning the reprint should be consistent with its content and the information in the disclosure cover sheet.

Practical Considerations

The draft guidance contemplates that, in appropriate circumstances, a single new controlled trial, a pharmacoepidemiologic study, or a rigorous meta-analysis could qualify for distribution to HCPs. This concession is significant, because those types of evidence would not normally satisfy the "substantial evidence" standard established by FDA's regulations—generally two, adequate and well-controlled clinical studies.

Nevertheless, the draft guidance places substantial limitations on the distribution of new risk information, and the safe harbor may be difficult to meet in practice. For example, the requirement that the publication be "at least as persuasive as the data sources that underlie the existing risk assessment" being rebutted, mitigated, or refined is ambiguous. In addition, it is unlikely that many peer-reviewed articles are written in a way that satisfies the requirement that the publication be a "fair characterization of all relevant information in the safety database." By the literal text of the draft guidance, only studies that address such contrary evidence can be distributed. It remains to be seen whether FDA will consider discussion of contrary evidence in the "cover sheet" sufficient in practice.

The draft guidance states that the reprints must be distributed separately from any promotional materials, and FDA implies the reprint itself does not qualify as promotional material. The draft guidance does, however, indicate that "a representative of the firm" may make statements concerning the reprint to the HCP as long as the statement is consistent with the reprint. Presumably, the ability of firm representatives to discuss the reprint includes sales representatives, who otherwise engage in promotional activities.

MIWG Citizen Petition Response

In July 2011, seven MIWG member companies filed a citizen petition requesting that FDA clarify its regulatory approach to four types of manufacturer communications about off-label uses: (1) responses to unsolicited requests; (2) scientific exchange; (3) communications with formulary committees and payers; and (4) the dissemination of third-party CPGs. In response, on December 28, 2011, FDA issued a draft guidance entitled "*Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*" and opened a public docket on the concept of "scientific exchange." In September 2013, MIWG member companies filed a second citizen petition requesting that FDA respond fully to all four requests in the July 2011 petition and further requesting that FDA undertake a comprehensive review and modification of its entire regulatory approach to manufacturer communications, particularly in light of three recent cases[4] highlighting the constitutional and statutory limitations of FDA's regulatory authority. In response to the 2011 and 2013 petitions, on February 28, 2014 FDA issued a draft guidance entitled "*Distributing Scientific and Medical Publications on Unapproved New Uses–Recommended Practices*."

In its June 6, 2014 response to the MIWG granting the petitions, FDA stated that it plans to issue guidance that addresses unsolicited requests, distributing scientific and medical information on unapproved new uses, and manufacturer discussions regarding scientific information more generally, by the end of the calendar year. In addition, FDA reported it plans to issue draft guidance documents that address MIWG's remaining requests involving health care economic information by year-end. The response also provided that, "in light of the importance of the public health issues and free speech and due process principles at stake," FDA commits to continuing the review of its regulatory regime for areas where it can refine and clarify the distinction between permissible and impermissible conduct.

It remains to be seen whether any regulatory changes made by FDA will result in additional flexibility or additional scrutiny over manufacturer communications regarding truthful, non-misleading information for approved or cleared products. It also remains to be seen whether FDA can square its current regulatory approach with constitutional requirements.

If you would like to discuss the foregoing or any related matter, please contact any member of Ropes & Gray's FDA regulatory practice or your usual Ropes & Gray advisor.

[4] *See Sorrell v. IMS Health, Inc.,*131 S. Ct. 2653 (2011); *FCC v. Fox Television Stations*, 132 S. Ct. 2307 (2012); *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).