In Pursuit of Evidence-Based Coverage: Navigating the FDA Regulatory Scheme in Communications with Payers

By Kellie Combs and Sarah Blankstein

As health care spending continues to rise, there is more pressure than ever on payers and other decision-makers to control costs. Pharmaceutical companies' communications with payers and formulary committees therefore play a necessary and increasingly important role in ensuring that these decision-makers have access to current, reliable information on which to base coverage decisions. Manufacturers often are the best source of this information, yet the over-breadth and ambiguity of FDA's regulatory scheme governing manufacturer speech chills many of them from sharing the types of information that payers consider to be among the most valuable. Incongruously, despite the constraints on manufacturer communications, other key stakeholders, including government and private payers, are subject to no such restrictions and routinely develop and disseminate all sorts of information with the aim of controlling health care costs. This article describes FDA's far-reaching, unclear, and asymmetrical regulatory scheme in the context of payer communications,[1]

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highlights a few of its practical implications, and calls for the agency to permit more flexibility in payer interactions.

The Deficiencies in FDA's Regulatory Regime

Notwithstanding FDA's repeated assertions that payer communications are within its purview,[2] FDA has not issued any regulations or guidance explicitly addressing communications with payers. The regulatory scheme addresses manufacturer communications more generally, including through the prescription drug advertising regulations, but it is a poor fit for payer interactions.

Indeed, the types of information payers need frequently do not align with the types of information FDA has traditionally permitted manufacturers to share. Payers often require information on investigational products and uses to ensure prompt coverage following FDA approval, as well as information on uses, dosage regimens, and patient populations that are not included in the approved product labeling. Manufacturers are chilled from proactively sharing such information, however, by FDA's prohibition on so-called "pre-approval promotion"[3]—a term that has never been defined—and the agency's interpretation of the FDCA's "unapproved new drug"[4] and "misbranding"[5] provisions to prohibit off-label promotion. Additionally, information of interest to payers often is derived from sources that would not meet the "substantial evidence" standard the agency has historically applied to promotional claims of safety and efficacy[6] and would not qualify as "adequate and well-controlled studies" under FDA's safe harbor for proactive dissemination of journal reprints that discuss off-label uses.[7]

FDA's *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* does permit manufacturers to respond to requests for off-label information from payers, but only when the requests are not "prompted in any way" and when the responses are provided in a "private, one-on-one communication."[8] The distinction between proactive, public communications on one hand, and reactive, private communications on the other, is suspect on First Amendment grounds,[9] and also impedes productive dialogue with payers, who in order to receive off-label information from manufacturers under the *Draft Guidance* must know what information to ask for and how to frame the question.

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In an attempt to open the channels of communication with payers,[10] Congress in 1997 enacted Section 114 of the Food and Drug Administration Modernization Act (FDAMA), which provides that the communication of health care economic information (HCEI) to formulary committees and other similar entities will not be considered false or misleading if it directly relates to an approved indication and is based on competent and reliable scientific evidence.[11] The impact of the statutory provision has been muted, however, because FDA has never issued any guidance to clarify its key terms.

The absence of clear regulations or guidance governing payer communications has not prevented FDA from issuing numerous warning and untitled letters to companies for alleged regulatory violations.[12] Many key stakeholders and experts in the field of health care delivery, including payers, prescribers, academic researchers, and members of industry, agree that the absence of regulations or guidance from FDA about FDAMA 114 or payer communications generally, in combination with the threat of government enforcement, has resulted in the underutilization of HCEI to the detriment of the public health.[13]

To facilitate guidance development, many have offered their own recommendations. Most recently, PhRMA and BIO jointly released their "Principles on Responsible Sharing of Truthful and Non-Misleading Information about Medicines with Health Care Professionals and Payers."[14] Anchored by the commitment to share science-based, contextualized data with health care professionals and payers in a truthful and non-misleading way, the Principles acknowledge that although the FDA-approved labeling should be a primary source of product information, other sources—including pharmacoeconomic analyses, pipeline and off-label information, and real-world evidence—are vitally important to patient access and appropriate care. The Principles also describe several hypothetical scenarios to illustrate how manufacturers should convey these types of information to payers, offering detailed guidance with respect to the disclosures that may be appropriate (e.g., related to study limitations, risk of bias, and regulatory status). The AMCP Partnership Forum, comprised of members from academia, industry, and the payer and provider communities, also recently weighed in, releasing consensus recommendations that addressed, inter alia, the audience with whom HCEI may be shared, permissible types of analysis and the applicable evidentiary standard, and

the extent to which the HCEI may vary from the product labeling.[15] Nevertheless, nearly 20 years after enactment of FDAMA 114, and despite multiple requests[16] and repeated agency promises,[17] FDA has never issued any guidance to clarify the provisions in FDAMA 114, much less to address payer interactions more generally.

Practical Implications for Payer Communications

The increasing emphasis on cost and value in the health care system—when juxtaposed with a regulatory scheme that is asymmetrical, unduly restrictive, and ambiguous—leaves manufacturers in a difficult predicament, compromises the ability of payers to make timely and well-informed decisions, and profoundly impacts patient care. There are numerous examples of communications that companies should unquestionably be permitted to engage in with payers, but over which FDA's current approach casts a cloud of uncertainty. Among them are:

1) *Communications about unapproved products or uses*: FDA regulations chill many manufacturers from sharing information about product candidates or new uses of approved products with payers prior to FDA approval for fear that the agency may view the communications as pre-approval "commercialization" or as promoting a new intended use. The restriction is especially problematic with respect to emerging therapies, where manufacturers are the best and often *only* source of clinical and pharmacoeconomic information required for coverage decisions, which are typically made well before the plan year begins.[18] A clear pathway for sharing information prior to approval is therefore critical to ensure that patient access to important and potentially life-saving therapies is not restricted or delayed.
2) *Communications that are not based on substantial evidence*: Although payers desire real-world and comparative data, such data rarely constitutes the "substantial evidence" required by FDA even for promotional communications that are fully consistent with the labeling.[19] Meta-analyses, observational studies, and certain other types of research, however, frequently do compare the risks and benefits associated with various products that are used to treat a certain disease or condition, yet the extent to which manufacturers may share this information proactively with payers has never been articulated.
3) *Responses to research in which a manufacturer's product was used in a way not contemplated in the product labeling:* Under FDA's regulatory regime, the single most determinative factor of whether information may be discussed is not the quality of the data or stakeholders' need for the information, but rather the identity of the speaker. Speakers aside from product manufacturers have free reign to discuss any form of evidence with any party, yet the ability of product manufacturers to respond proactively is uncertain at best. In addition to the grave First Amendment concerns raised by this asymmetry,[20] this framework has significant consequences for payers, prescribers, and patients.

Consider, for example, a hypothetical scenario in which a government actor analyzes Medicare claims data to develop comparative effectiveness research (CER) about products commonly used to treat high cholesterol in the general population, one of which is "Product X," a drug with an indication specifically limited to treatment of patients with a previous history of cardiovascular events. If the CER concludes that Product X is associated with higher incidence of adverse events than other therapies—a result flatly contradicted by other, higher-quality data—the manufacturer may fear that proactive rebuttal of the CER could be viewed by FDA as a claim that Product X is safe or effective for an off-label use.

The Path Forward

With each passing year, there is building consensus that the FDA regulatory scheme governing payer communications is unclear, unworkable, and subject to constitutional challenge. Payers, members of industry, and other key stakeholders have offered a number of suggestions to address the flaws in FDA's current system and, due to their varied interests, may have different ideas of how best to allow additional flexibility while protecting the public health. While the correct approach may be debated, to ensure that that payers have access to the wide range of evidence necessary to make informed coverage decisions and that patients have access to the therapies that they need, the time has come for prompt, meaningful reform.

1. Our focus on payer communications in this article should not be interpreted to mean that FDA's regulatory scheme as applied to manufacturer communications with prescribers or other individuals does not suffer from similar infirmities. Moreover, we note that the agency has jurisdiction to regulate payer interactions only to the extent they qualify as advertising, labeling, or evidence of intended use, as those terms are properly construed pursuant to the Food, Drug, and Cosmetic Act (FDCA) and in light of First Amendment principles protecting the right of

manufacturers to engage in truthful, non-misleading speech. *See, e.g.*, Sorrell v. IMS Health, Inc., 131 S. Ct. 2653 (2011); United States v. Caronia, 703 F.3d 149 (2d Cir. 2012); Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

2. *See e.g.*, Division of Drug Marketing, Advertising, and Communications (DDMAC), Current Issues and Procedures (Apr. 1994) (characterizing formulary kits as promotional labeling); *see also* DDMAC, Principles for the Review of Pharmacoeconomic Promotion (Draft), 1 (Mar. 1995) (applying the "substantial evidence" requirement for promotional claims to the communication of pharmacoeconomic information).
3. 21 C.F.R. § 312.7.
4. 21 U.S.C. § 355(a) (prohibiting the introduction in interstate commerce of any unapproved new drug).
5. 21 U.S.C. § 352(f) (deeming a drug misbranded if its labeling fails to provide "adequate directions for use").
6. 21 C.F.R. § 202.1(e)(6) (applying the substantial evidence standard to promotional claims); *see also* 21 C.F.R. § 314.126 (describing characteristics of an adequate and well-controlled study).
7. *See* FDA, *Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (2014), at 7.
8. FDA's *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (2011).
9. *See Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d at 224-26.
10. *See* S. Rep. No. 105-43 (1997), 1997 WL 394244 at *42-43; H.R. Rep. No. 105-310 (1997), at 65.
11. 21 U.S.C. § 352(a).
12. *See, e.g.*, FDA Untitled Letter to Abbott Laboratories (Jan. 22, 2009) (letter based on formulary flashcard for Depakote); FDA Warning Letter to Cephalon, Inc. (Feb. 27, 2007) (letter based on handout for Provigil disseminated at formulary committee presentation); FDA Untitled Letter to Glaxo Wellcome (Apr. 28, 2000) (letter based on a Lotronex formulary kit); Untitled Letter to Burroughs Wellcome Company (Dec. 2, 1994) (letter based on pre-approval mailings and presentations to managed care organizations about investigational drug, lamotrigine).
13. *See generally, e.g.*, AMCP Partnership Forum, *FDAMA Section 114—Improving the Exchange of Health Care Economic Data*, 22 J. of Managed Care & Specialty Pharmacy 826 (2016) (AMCP Partnership Forum); Memorandum from the Medical Information Working Group (MIWG) to L. Kux, Asst. Comm'r for Policy, FDA, *Use of Health Care Economic Information Under Section 114 of the Food and Drug Administration Modernization Act* (Oct. 31, 2014) (MIWG FDAMA 114 Memorandum); *see also* PhRMA, *White Paper: The Development and Dissemination of Health Care Economic Data to Payors, Formulary Committees, or Other Similar Entities* (Aug. 14, 2012); Peter J. Neumann, *What Ever Happened to FDAMA Section 114? A Look Back After 10 Years*, 12 Value in Health 189 (2009).
14. PhRMA & BIO, *Principles on Responsible Sharing of Truthful and Non-Misleading Information about Medicines with Health Care Professionals and Payers* (2016).
15. *See generally* AMCP Partnership Forum, *supra* note 13.
16. *See, e.g.*, MIWG FDAMA 114 Memorandum, *supra* note 13; MIWG Citizen Petition, Docket No. FDA-2013-P-1079 (Sept. 3, 2013); MIWG Citizen Petition, Docket No. FDA-2011-P-0512 (July 5, 2011).
17. *See, e.g.,* Letter from Leslie Kux, Assistant Commissioner for Policy, FDA to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014); Letter from Leslie Kux to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (Dec. 22, 2014).
18. *See generally*, Eli Lilly Company and Anthem, *Facilitating Open Communication about Emerging Therapies* (Jan. 29, 2016); *see also* Caitlin Owens, Insurers, *Drugmakers Want to Exchange Info on Specialty Drugs*, Morning Consult (Apr. 19, 2016).
19. 21 C.F.R. § 202.1(e)(6) (applying the substantial evidence standard to promotional claims); *see also* 21 C.F.R. § 314.126 (describing characteristics of an adequate and well-controlled study).
20. *See Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2667 (2011) (holding that content- and speaker-based restrictions are subject to heightened scrutiny).