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COMMENTS OF THE MEDICAL INFORMATION WORKING GROUP ON SCIENTIFIC EXCHANGE (DOCKET NO. FDA-2011-N-0912) AND RESPONSES TO UNSOLICITED REQUESTS (DOCKET NO. FDA-2011-D-0868)

The Medical Information Working Group (MIWG) hereby submits these comments on (1) the notice published in the Federal Register on December 28, 2011 (76 Fed. Reg. 81,508), inviting comments on scientific exchange, and (2) the draft guidance on responses to unsolicited requests, published in the Federal Register on December 30, 2011 (76 Fed. Reg. 82,303). The MIWG is a coalition of prescription drug and medical device manufacturers seeking clarity in the federal regulatory paradigm for the dissemination of information relating to investigational products and new uses of lawfully marketed medical products.[1] We thank FDA for establishing the scientific exchange docket and proposing new guidance on unsolicited requests, and look forward to learning more about the other initiatives to which the December 28 notice refers to improve the rules applicable to manufacturer dissemination of information relating to new products and uses.

Several members of the MIWG submitted the July 5, 2011, citizen petition to which the December 28 notice refers. The petition asks FDA to clarify the rules governing manufacturer communication of information about new uses and unapproved, uncleared products by promulgating binding regulations with respect to four types of off-label communications—responses to unsolicited requests for medical information, scientific exchange, distribution of clinical practice guidelines, and communications with payers. With regard to responses to unsolicited requests, FDA's draft guidance creates a new definition of "solicited," and distinguishes "public" from "non-public" requests. On these points, we support the comments of Pharmaceutical Research and Manufacturers

[1] The following companies are currently members of the MIWG: Allergan, Inc.; Amgen Inc.; Bayer Healthcare Pharmaceuticals, Inc.; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline LLC; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Novo Nordisk, Inc.; Pfizer, Inc.; Purdue Pharma L.P.; and sanofi-aventis U.S. LLC.

of America (PhRMA), and respectfully request that the Agency abandon its "public" and "non-public" distinction and more narrowly define the concept of solicitation.

As to scientific exchange, the petition asks FDA to revise 21 C.F.R. § 312.7 to specify additional forms of permitted communication based on prior preamble language and to recognize scientific exchange in the medical device context. In response, FDA's December 28 notice sets forth thirteen questions and invites "detailed comment on all aspects of scientific exchange communications and activities related to off-label uses of marketed drugs, biologics, and devices and use of products that are not yet legally marketed."[2] Rather than respond to each of those questions, we focus our comments on the following key points:

- First, we renew the citizen petition's request for clarity to the extent that clarity can be provided without sacrificing critically important public health, constitutional, and statutory principles. Highly restrictive rules on scientific exchange would harm the public health, violate the First Amendment, and exceed the scope of FDA's statutory authority.

- Second, we believe that FDA should seek to clarify key definitions in the areas in which it has statutory authority rather than purporting to define the conduct over which it lacks such authority. Specifically, FDA should focus its efforts on clarifying the scope of key statutory provisions, such as the "labeling" and "advertising" definitions, that determine the extent of the agency's regulatory authority. We do, however, agree with the July 5 citizen petition that the 1987 preamble language set forth in the petition and reproduced in the December 28 notice represents a sound approach to defining scientific exchange.[3]

- Third, although we have reservations about a wholesale reconsideration of the scope of permissible scientific exchange, we have set forth in an accompanying appendix a non-exclusive list of activities and communications that we believe are properly regarded as scientific exchange in an effort to assist the Agency.

[2] 76 Fed. Reg. at 81,509 (emphasis added).
[3] 52 Fed. Reg. 19,466, 19,475 (May 22, 1987). The language recommends that manufacturers making statements about investigational new drugs (1) make clear that the drug is investigational, (2) make no claims that the drug has been proven to be safe or effective, and (3) assure that their statements are truthful and non-misleading "when measured against available information on the drug . . . as set forth in materials such as investigators' brochures . . . ." It would be necessary, in adopting the approach reflected in this language, to explain the meaning of "claims" in the second criterion, and extend the approach reflected in the language so that it also explicitly covers new uses (in addition to investigational products) and medical devices.

I. MEDICINE, LIKE OTHER FIELDS OF SCIENTIFIC ENDEAVOR, REQUIRES FREE INTERCHANGE AMONG MULTIPLE VIEWPOINTS OVER TIME

"[O]pen debate is an essential part of both legal and scientific analyses. . . . Scientific conclusions are subject to perpetual revision. . . . The scientific project is advanced by broad and wide-ranging consideration of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so, and that in itself is an advance."[4] Science is cumulative, iterative, and self-correcting: each individual discovery is founded on the work of, and is subject to analysis and criticism from, others. Scientific and medical progress depends on the free flow of information about past discoveries, and on the comments, analyses, criticism, and other findings associated with those discoveries. The system, to operate effectively, requires the robust participation of multiple speakers reflecting differing points of view.[5]

Scientists practice "a discipline that seeks, but never finds, absolute truth," using a "variety of criteria to evaluate data in conditions that provide less than total certainty."[6] An opinion that is "regarded as valid" at a particular moment in time can become "invalid" if additional information emerges that conflicts with the earlier information or opinion and is "more credible."[7]

"Physicians," in particular, "must make decisions in the face of uncertainty and without . . . [the] luxury of awaiting further information."[8] Because of the nature of clinical practice, they must rely on a wide range of information sources and, critically, on their own judgment in weighing those sources given the circumstances of a particular case. The medical and scientific literature on which physicians commonly rely contains conflicting observations, uncertain conclusions, retractions, and public challenges. The findings of one study may be replicated by a subsequent study, or may be discredited, and often seemingly disparate data sets are reconsidered in the secondary literature (e.g., systematic reviews).

Whereas physicians consider a multitude of information sources and rely on their own judgment and experience in making treatment decisions, regulatory

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[4] Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 596-97 (1993).

[5] "[T]he constant process of questioning, testing, updating, and sometimes replacing received wisdom is the hallmark of good science . . . ." Eugene Volokh, In Defense of the Marketplace of Ideas, 97 Va. L. Rev. 595, 597 (2011).

[6] Brief amici curiae of Professors Kenneth Rothman, Noel Weiss, James Rocins, and Raymond Neum, 61 U.S.L.W. 3284 (1992), in Daubert v. Merrell-Dow Pharmaceuticals Inc., 509 U.S. 579 (1993).

[7] 21 C.F.R. § 202.1(e)(6)(iii). The regulatory standards for the adjudication of clinical trials as sources of efficacy data for new drugs make explicit that those investigations are properly evaluated according to contemporary scientific standards; as knowledge regarding trial design evolves, so too does FDA's approach to the regulatory review of those data sources. Id. § 314.126.

[8] Lars Noah, Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community, 44 Ariz. L. Rev. 373, 382 (2002).

authorities consider data derived from a much narrower range of sources—mainly, randomized controlled trials (RCTs). After FDA has "judg[ed] the safety and effectiveness of drugs and the truthfulness of their labeling," health care practitioners are "responsible for making the final judgment as to which, if any, of the available drugs" will be prescribed "in the light of the information contained in their labeling and other adequate scientific data available . . . ."[9] As the Director of the Center for Drug Evaluation and Research put it: "How do you generate knowledge that you can rely on? . . . I think there are very different opinions about that in different sectors. The regulators come down on pretty reliable data and inferences because we make decisions that are big regulatory decisions. If you are a payer or an individual practitioner, you make decisions . . . based on other considerations and that is reasonable."[10] Because medical practice requires making judgments beyond the clinical trials leading to regulatory approval, clinicians must often consider information from non-regulatory sources.

From FDA's perspective, approved labeling serves as the source of permissible statements in promotional labeling and advertising.[11] Yet labeling does not always contain the most up-to-date (or even the most accurate) information about the use of a medical product.[12] For physicians to use their "best knowledge and judgment" in the use of approved drugs,[13] they must have access to information that has not been reviewed by FDA or set forth in approved labeling. Manufacturers often have unique access to information of great public health importance, and also often the ability and the incentive to advance the scientific process through contributions to scientific

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[9] 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972).

[10] Drug Developers Facing "Unsettled" Period of 5 to 10 Years as CER Environment Evolves, FDA's Woodcock Says, The Pink Sheet (June 28, 2010) (quoting Janet Woodcock). Even the population-level judgments reached by FDA are the subject of disagreement, and indeed, "the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others." CDER & CBER, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998); see also SOPP 8006: Resolution of Differences in Scientific Judgement in the Review Process (Jan. 15, 2009) ("Differences in scientific opinion can occur regarding the interpretation and/or application of information pertinent to the regulatory process. . . . Differences in scientific opinion or perspective are an expected part of any scientific review or regulatory process."). Moreover, as FDA has long recognized, the regulatory assessment of risks and benefits often changes after approval, sometimes dramatically, based on information obtained from clinical use. 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) (Results of treatment obtained outside of adequate and well-controlled trials "may be helpful to patients and physicians as well as to" FDA, and can lead to warnings against dangerous unapproved uses or "acceptance of previously unknown uses.").

[11] 21 C.F.R. § 202.1(e)(4) ("An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the act after October 10, 1962 . . . shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application . . . .").

[12] Labeling "cannot be both authoritative and avant garde." Robert Temple, Legal Implications of the Package Insert, 58 Med. Clinics of N. Am. 1151, 1155 (1974).

[13] 44 Fed. Reg. 37,434, 37,435 (June 26, 1979).

exchange and investments in the processes of science themselves.[14] Scientific exchange therefore must not—and, as a constitutional matter, cannot—be restricted.

II. FIRST AMENDMENT PROTECTION OF SCIENTIFIC EXCHANGE REFLECTS ITS PUBLIC HEALTH IMPORTANCE

Robust scientific exchange about investigational products and new uses of lawfully marketed products is fully consistent both with FDA's vital public health mission and with First Amendment principles. This past Term, in Sorrell v. IMS Health Inc., the Supreme Court held that First Amendment protection is particularly vital "in the fields of medicine and public health, where information can save lives." 131 S. Ct. 2653, 2664 (2011).[15] By aligning its regulatory scheme with constitutional limitations, FDA can also assure an appropriate role for manufacturer speech in supporting sound medical practice.

It has, for many years, been beyond dispute that "core" scientific speech is entitled to robust protection under foundational First Amendment principles. "Scientific" speech "reside[s] at the core of the First Amendment." Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 62 (D.D.C. 1998); Bd. of Trs. v. Sullivan, 773 F. Supp. 472, 474 (D.D.C. 1991) ("[T]he First Amendment protects scientific expression and debate just as it protects political and artistic expression."); Miller v. California, 413 U.S. 15, 34 (1973) (The First Amendment protects speech that has "serious . . . scientific value"). Scientific exchange is precisely the type of expression that is entitled to the highest level of First Amendment protection. Miller, 413 U.S. at 34. Even if regulations governing scientific exchange were evaluated according to a more forgiving standard, however, Sorrell makes clear that regulatory regimes that disfavor certain speakers or viewpoints are subject to "heightened scrutiny."

Sorrell makes clear that, where a law restricts truthful, non-misleading speech on the basis of its content and the identity of the speaker, that law "must be subjected to heightened judicial scrutiny," even if the speech is characterized as "commercial." See 131 S. Ct. at 2664 (holding that "[c]ommercial speech is no exception" to the heightened judicial scrutiny applicable to speaker- and content-based speech restrictions); id. at 2667 (holding that if a law "imposes a speaker- and content-based burden" on commercial speech, "that circumstance is sufficient to justify application of heightened scrutiny"). Under Sorrell, content- and speaker-based restrictions on commercial speech will fail heightened judicial scrutiny "[i]n the ordinary case." Id. at 2667.

[14] Hearing on S. 1944 Before a Subcomm. of the S. Comm. on Commerce, 73d Cong. 10 (1933) ("There is no disposition to write anything into the bill to interfere with progress.") (statement of Commissioner Campbell).

[15] Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 73 (D.D.C. 1998) (truthful information about medical products "may be life saving information, or information than makes a life with a debilitating condition more comfortable.").

The relevance of Sorrell to scientific exchange and responses to unsolicited requests is plain: the decision dispels any remaining notion that FDA is free to regulate manufacturer dissemination of information about investigational products and new uses without constitutional limitation. Although Sorrell itself did not deal with the FDCA, in his dissenting opinion Justice Breyer acknowledged that the majority opinion implicated FDA's regulatory framework because it, too, imposes "speaker-based" restrictions on speech. Id. at 2678 (Breyer, J. dissenting).

The First Amendment limits the government's power to suppress truthful, non-misleading speech relating to lawful activities such as off-label use. "If the First Amendment means anything," it means that suppressing such speech "must be a last—not first—resort." Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002). Society has a "strong interest in the free flow of commercial information." Va. St. Bd. of Pharm. v. Va. Cit. Cons. Council, 425 U.S. 748, 764 (1976). The First Amendment requires the government "to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them. . . . It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us." Id. at 770; see W. States, 535 U.S. at 374 ("We have previously rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information."). "The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good.'' 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996) (plurality op.) (citation omitted). FDA, no less than any other government entity, must adhere to these constitutional principles. See R.J. Reynolds Tobacco Co. v. FDA, Civ. No. 11-1482, at 18 (RJL) (D.D.C. decided Feb. 29, 2012) ("Congress must pass laws, and the FDA must implement final rules, that are consistent with the requirements of the Constitution.").

FDA must assure the applicable rules are appropriately tailored and well-defined to avoid chilling manufacturer speech. "Because First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity." Keyishian v. Bd. of Regents of the U. of N.Y., 385 U.S. 589, 604 (1967); Reno v. ACLU, 521 U.S. 844, 874 (1997). The First Amendment requires speech restrictions to be clear and precise, because "[u]ncertain meanings inevitably lead citizens to 'steer far wider of the unlawful zone' than if the boundaries of the forbidden areas were clearly marked." Grayned v. City of Rockford, 408 U.S. 104, 109 (1972) (quoting Baggett v. Bullitt, 377 U.S. 360, 372 (1964)). The Government cannot ban broad swathes of speech without specifying the limitations and the basis for doing so. "The test is whether the [restriction] affords the precision of regulation that must be the touchstone in an area so closely touching our most precious freedoms." Buckley v.

Valeo, 424 U.S. 1, 41 (1976) (internal quotation marks omitted); see Nat'l Ass'n of Mfrs. v. Taylor, 582 F.3d 1, 22–23 (D.C. Cir. 2009).

A series of ongoing cases likely will further explicate the precise ways in which First Amendment principles affect FDA's regulation of manufacturer speech. In the meantime, however, FDA can help assure that its approach to the regulation of speech respects constitutional limitations and recognizes the high value of scientific exchange in medical practice. FDA does not have the option of simply implementing the FDCA despite obvious constitutional infirmities on the ground that the agency cannot "second-guess Congress."[16] Rather, "Congress must pass laws, and the FDA must implement final rules, that are consistent with the requirements of the Constitution."[17]

In recent First Amendment litigation, FDA has recognized[18] important limiting principles:

1. FDA does not regulate "promotion," but rather has authority with respect to "labeling" and "advertising"—statutorily defined categories that together are sometimes more conveniently referred to as "promotion." Press releases are not subject to regulation as "labeling."

2. Statements that do not prescribe, recommend, or suggest a use are not subject to regulation by FDA. Consequently, a manufacturer is entitled to (among other things) provide "appropriate warnings about the adverse consequences of an off-label use," and doing so does not "trigger[] the prohibitions on distributing a product for an unapproved use and misbranding a product for failure to provide adequate directions for use."

3. "Intended use" is not created merely by a "manufacturer's knowledge that an approved product was being prescribed by doctors" for a new use; by the fact that a physician to whom "on-label" use information is being provided also can or even frequently does encounter clinical scenarios in which a product could be used "off-label"; or by the manufacturer's practice of teaching its representatives about potential off-label uses.

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[16] U.S. Opp. to Pl.'s Mot. for Prelim. Injunct., R.J. Reynolds Tobacco Co. v. FDA, No. 11-1482 at 32 (D.D.C. filed Sept. 9, 2011).

[17] R.J. Reynolds Tobacco Co. v. FDA, Civ. No. 11-1482, at 18 (RJL) (D.D.C. decided Feb. 29, 2012).

[18] Decl. of Dr. Rachel Sherman ¶ 14, Par Pharmaceutical v. United States, No. 11-1820 (D.D.C. Jan. 1, 2012); Transcript of Cross Examination of Sandeep Saini, United States v. Stevens, No. RWT-10-694, at 89 (D. Md. Apr. 27, 2011); Decl. of Dr. Robert Temple ¶¶ 9-10, Allergan v. United States, No. 09-1879 (D.D.C. Dec. 11, 2009); Allergan v. United States, Gov't Summ. J. Br. 9; Gov't Summ. J. Reply 6, 9; U.S. Opp. to Def's Mot. to Dismiss, United States v. Harkonen, No. 08-164 at 8, n.3 (N.D. Cal. Apr. 20, 2009).

4. FDA's off-label promotion restrictions do not prohibit manufacturers from teaching paid speakers about potential off-label uses, and do not prevent those speakers from discussing off-label uses, so long as the information shared is in response to the unsolicited question of an audience member.

These statements should be incorporated directly into the relevant regulatory provisions to help align the regulatory scheme with constitutional limitations.

III. THE FDCA APPLIES TO PARTICULAR FORMS OF MANUFACTURER COMMUNICATION EXPRESSLY IDENTIFIED IN THE STATUTE

As discussed above, by its very nature, scientific exchange occupies a critically important role in clinical decision making by supplementing the authoritative safety and efficacy information set forth in FDA-cleared or –approved labeling. Because of its societal value, scientific exchange has long been recognized as residing at the core of First Amendment-protected speech, and the Supreme Court has recently recognized that manufacturer speech is subject to a high level of protection even when it is commercial in nature. Scientific exchange is also outside the scope of FDA's authority under the "labeling" and "advertising" provisions of the FDCA.[19]

The scope of the "labeling" definition in the FDCA is central to FDA's authority to regulate manufacturer speech because it is the touchstone of key statutory provisions, such as the "new drug" and "adequate directions" requirements.[20] The FDCA establishes specific requirements and specific prohibitions for the content of "labeling."

Section 502(a) provides that "A drug or device shall be deemed to be misbranded—. . . If its labeling is false or misleading in any particular." 21 U.S.C. § 352(a). For this provision to apply, a false or misleading statement must appear in a communication that qualifies as "labeling." According to section 505(a) of the FDCA, "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) [new drug application (NDA)] or (j) [abbreviated new drug application (ANDA)] is effective with respect to such drug." Id. § 355(a). Whether a product is a "new drug" depends on the content—in particular the "conditions prescribed, recommended, or suggested"—of its labeling. Id. § 321(p)(1); see also id. §§ 360(k), 351(f)(1)(B), 352(o), 360e(a)

[19] Even remedial statutes cannot be interpreted without limitation. See, e.g., Brown & Williamson v. FDA, 529 U.S. 120, 161 (2000) ("[N]o matter how important . . . the issue, . . . an administrative agency's power to regulate in the public interest must always be grounded in a valid grant of authority from Congress.") (internal quotes and citation omitted); United States v. Article of Drug . . . Bacto-Unidisk, 394 U.S. 784, 800 (1969) ("'[I]n our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop.'") (quoting 62 Cases of Jam v. United States, 340 U.S. 593, 600 (1951)).

[20] 21 U.S.C. §§ 321(p), 355(a), 352(f)(1).

(counterpart device provisions). Section 502(f)(1) of the FDCA provides that a drug or device "shall be deemed to be misbranded" unless its labeling contains "adequate directions for use." Id. § 352(f)(1).[21]

The FDCA defines "labeling" to mean "written, printed, or graphic matters" upon the article or "any of its containers or wrappers," or "accompanying such article." 21 U.S.C. § 321(m), (k). The Supreme Court in Kordel v. United States addressed whether written material could "accompany" a drug, and thus qualify as labeling, even when it was distributed separately from the package. 335 U.S. 345, 348 (1948). The Court held that written materials comprise "labeling" when they: (1) have the same origin as the drug; (2) have the same destination; (3) are designed for use in the sale and distribution of the drug; and (4) have a "textual relationship" or "constitute[] an essential supplement" to the label. Id. at 348, 350 (emphasis added). As subsequent decisions have explained, "labeling does not include every writing which bears some relation to the product. There is a line to be drawn, and, if the statutory purpose is to be served, it must be drawn in terms of the function served by the writing." United States v. An Undetermined Number of Cases . . . "Sterling Vinegar and Honey . . . ," 338 F.2d 157, 158-59 (2d Cir. 1964).

FDA has acknowledged that the list of items included in the regulation that is often cited as a definition of "labeling," 21 C.F.R. § 202.1(l)(2), is not a straightforward regulation of definition but rather operates to exclude certain forms of manufacturer communication from the scope of the advertising provisions of the FDCA and FDA regulations.[22] The only applicable legal definition of labeling therefore arises out of the statutory text itself (21 U.S.C. § 321(m)), a general regulatory definition of labeling in 21 C.F.R. Part 1 (§ 1.3(a)), and relevant case law. Properly construed, FDA's "labeling" authority does not reach manufacturer communications such as press releases, reprints (whether "on-label" or "off-label"), or indeed anything that does not (among other criteria) function as an essential supplement to the label for the product.

The scope of the "advertising" definition is similarly limited. Although the statute itself does not include a definition, it is clear that "advertising" refers to forms of

[21] The concept of "intended use" is closely related to the scope of FDA's authority under the "labeling" provisions. The two are linked by Section 502(f)(1) and FDA implementing regulations, 21 C.F.R. §§ 201.5, 801.5, 201.128, 801.4, which define "intended use" to reach "expressions." To assure appropriate latitude for scientific exchange, FDA must clarify the scope of its intended use regulation to reflect the authoritative legislative history and the relevant case law. See S. Rep. No. 361, 74th Cong., 1st Sess. 4 (1935) ("The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put."); Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) ("no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use") (citing Coyne Beahm v. FDA, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997)), aff'd on other grounds, 529 U.S. 120 (2000).

[22] Def.'s Summ. J. Reply at 22-23, Allergan v. United States, No. 09-1879 (D.D.C. filed Mar. 29, 2010).

manufacturer speech that are "published" or "broadcast"—references that clearly reflect FDA's recognition of the need to truncate required disclosures because space for them may not be practicable in many media. 21 C.F.R. § 202.1(l)(1).[23]

The FDCA carefully limits the scope of manufacturer communications about regulated products and does not reach "communications and activities" generally (as stated in the December 28 notice) or any and every manufacturer statement that names a product, bears a "textual relationship" with a product, or "effectively promotes" a product.[24] FDA cannot regulate the content of any communication that falls outside the scope of the "labeling" and "advertising." Properly construed, the FDCA provisions delineating FDA's authority over manufacturer speech do not reach scientific exchange (such as the specific activities set forth in the accompanying appendix).[25]

[23] Nothing in the FDCA was intended to interfere with a manufacturer's ability to provide emerging efficacy information to physicians. Hearing on S. 2800 Before the S. Comm. on Commerce, 73d Cong. 114 (1934) ("Well, isn't it right that the medical profession should have this progressive thought as early as possible, even though it might not yet be thoroughly established on a scientific basis? . . . [T]he purpose of the original writer of the bill—this was in the original bill—was to make it possible for the medical profession to receive even those glimmerings of hope that are held out by the scientific research men, and I am inclined to think that it is right that they should have that information. . . . [Y]ou take some great research laboratory, that will do a lot of work in connection with one of these diseases—we will say goiter, or nephritis, or high blood pressure, or something like that—it develops what in the laboratory appears to be something worthwhile. It gives that information to the profession.") (remarks of Sen. Copeland). The Drug Amendments of 1962 were intended to require a modest disclosure—a "true statement" in "brief summary" of efficacy information—in drug advertising, not to "censor" it. E.g., Hearings on S. 1552 Before the S. Subcomm. at 192 (colloquy between Dr. May and Sen. Kefauver) ("Dr. May. . . . As I understand S. 1552, there are no censorial powers that would check many prevalent shortcomings in promotion. . . . . Sen. Kefauver. That is true. It does do this though—it requires that in advertisements . . . the claims as to what the drug will do and also the adverse side effects, in summary form at least, be sent to the doctors . . . but it does not undertake to set up a board of censors as to what the advertising should be.").

[24] These "rules of thumb" have been used to describe the range of communications over which FDA has authority. See, e.g., Regulating Prescription Drug Promotion, Statement of Janet Woodcock, M.D., Dir., CDER, Senate Special Committee on Aging (July 22, 2003) ("'Product-claim' ads are regulated by FDA and are those ads which generally include both the name of a product and its use, or make a claim or representation about a prescription drug."); FDA, Draft Guidance for Industry: "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms, at 8 (Jan. 2004) (referring to "textual relationship" standard); Letter from Christine Hemler Smith, Pharm. D., DDMAC to John R. Cutt, Ph.D., Novartis Pharmaceuticals Corp. (June 27, 2003) ("effectively promotes"). That FDA has used so many formulations in an effort to explain the scope of its power, and that these statements have changed over time, illustrates the need for clarity in this area.

[25] Other examples of manufacturer speech not subject to FDA regulation include public relations activities, patent applications, securities filings, statements to analysts, and testimony in government proceedings (including communications with regulators, legislators, and courts).

IV. CONCLUSION

Because of the societal importance of scientific exchange, FDA's policy development in this area should focus on providing clear definitions of key statutory and regulatory provisions that determine the extent of the agency's authority. FDA should not seek to "regulate," through the establishment of non-binding "guidance" or "recommendations" or otherwise, in areas in which it lacks statutory authority. Because scientific exchange is not within the labeling and advertising provisions of the FDCA and cannot provide "evidence of intended use," it is not subject to regulation by FDA, and FDA should not seek to engage in a comprehensive reevaluation of the extent to which the Agency might deign to permit it.

Assertions of sweeping FDA regulatory authority over manufacturer speech are not now and indeed have never been consistent with the FDCA. Nor have they adequately reflected First Amendment limitations. FDA should take the opportunity provided by important developments in the case law to revise its approach to the regulation of manufacturer speech.[26] In so doing, FDA must recognize that it cannot and should not regulate scientific exchange—because of limitations imposed by the First Amendment and by the statute, and in recognition of the need for the unfettered flow of information about scientific developments, in medicine as in other areas of scientific endeavor.

[26] In the past, FDA has advanced First Amendment positions that clearly need to be revisited, particularly in view of recent judicial decisions. See, e.g., 59 Fed. Reg. 395, 422 (Jan. 4, 1994) (asserting that agency regulations are valid "under the limited scrutiny that has been afforded restrictions on speech under extensive regulatory schemes involving areas of economic activity").

Respectfully submitted,

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APPENDIX
PRACTICES THAT CONSTITUTE SCIENTIFIC EXCHANGE

Below, we describe by way of example several practices that comprise neither labeling nor advertising and do not provide "evidence of intended use." These practices, along with those described in the Citizen Petition (i.e., dissemination of third-party clinical practice guidelines and communication with payers, formulary committees, and similar entities[27]) and a wide variety of others, have never been addressed by FDA in any binding or comprehensive fashion.[28] Consistent with the statutory and First Amendment analyses above, these practices are not subject to FDA regulation. For clarity's sake, however, we ask FDA to explicitly recognize in binding regulations that such communications and activities constitute permissible scientific exchange so long as: (1) the information is truthful and non-misleading;[29] (2) the manufacturer clearly states that the product or use that is the subject of the communication is not approved by FDA; and (3) the manufacturer makes no claims that the product or use has been proven safe or effective.[30]

1. Communication of Information About Risks Of New ("Off-Label") Use

Health care professionals, to make informed treatment decisions with their patients, must have access to up-to-date scientific information, particularly risk information, even if the information concerns an "off-label" use. Manufacturers are superior repositories of information about their products,[31] systematically collecting, organizing, analyzing, and retaining information that is often of a type and quality relied on by physicians in the exercise of their medical judgment, and in many cases, relates to unapproved as well as approved uses of the manufacturers' products.[32] Although

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[27] Payer communications continue to be a critical area of concern for manufacturers. Included within this category would be the submission of dossiers to managed care organizations and the like, regardless of whether a "standing unsolicited request" was in effect.

[28] Indeed, the only activities explicitly characterized by FDA as scientific exchange are publishing results of "scientific studies, letters to the editor in defense of public challenges, [and] investigator conferences." See 52 Fed. Reg. at 19,475. We ask that FDA confirm in binding regulations the status of these communications as scientific exchange.

[29] As described in Section I, supra, the scientific process is dynamic and self-correcting, and hypotheses and conclusions initially deemed to be accurate may later be deemed incorrect. The possibility that a scientific statement may ultimately be disproven does not undermine its "truthfulness" so long as the statement is factual and is not promotional, and the underlying research being discussed was derived using appropriate scientific methodology.

[30] These criteria reflect the parameters previously outlined by FDA. See 52 Fed. Reg. at 19,475.

[31] See, e.g., Wyeth v. Levine, 129 S. Ct. 1187, 1202 (2009) ("[M]anufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.").

[32] Indeed, FDA requires a manufacturer to review and analyze all information it obtains regarding adverse events associated with its products, regardless of source and regardless of whether the events involved an off-label, as opposed to an on-label, use. See 21 C.F.R. § 314.80(b)–(c). FDA also requires manufacturers to analyze all information obtained about the safety of a drug from any source, regardless

product labeling may warn of adverse events associated with certain off-label uses or discourage the uses altogether, manufacturers are chilled from informing physicians about how to minimize or avoid risks associated with the off-label uses of their products (e.g., by altering the dose of the product) even when the off-label use represents the standard of care.[33] This chill arises from understandable concern on the part of manufacturers that FDA and DOJ prosecutors may treat any manufacturer-provided direction on how to use a drug or device safely off-label as impermissible promotion of an off-label use. [34] We ask that FDA, in recognition of the public health importance of such information, explicitly affirm that such communication constitutes scientific exchange.

2. Medical Science Liaisons

Manufacturers often bifurcate their field-based personnel into sales representatives and medical representatives. The role of the medical representative, often referred to as a medical science liaison (MSL), is to act as a scientific expert who can provide scientific information to prescribers, clinical investigators, and other health care professionals. Unlike sales representatives, MSLs are not tasked with selling product, are not compensated as sales representatives based on the sale of any particular products, and report to the scientific affairs, medical affairs, or clinical development arms of their companies.[35] As medical professionals, most of whom hold an advanced postgraduate degree, such as an MD, PhD, or PharmD.,[36] their tasks center around conveying complex medical and technical information to health care providers, keeping abreast of relevant scientific developments, representing the manufacturer at scientific symposia and meetings, supporting clinical trials by identifying

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of whether it pertains to an on- or off-label use. See 21 C.F.R. § 314.50(d)(5)(iv); see also Ethan M. Basch, et al., Potential Pharmaceutical Manufacturer Sponsorship and Drug Information, 161 Arch. Internal Med. 2625, 2625-26 (2001).

[33] One circumstance where the problem is particularly evident is where a product is used off-label by physicians in a medical specialty other than the one associated with the labeled indication(s). In this circumstance, companies may risk a criminal investigation if their representatives so much as appear in the medical offices of the physicians who specialize in the off-label condition—even if only for the purpose of discussing a safety concern. The risk arises because the government may seize upon such presence alone to allege an intent on the manufacturer's part that the drug or medical device in question be used for the off-label condition (See Allergan v. United States, Gov't Summ. J. Br. at 36).

[34] Although FDA has stated that it does not construe the FDCA and accompanying regulations as prohibiting the communication of information regarding the risks associated with an off-label use of a product if that information is "non-promotional" (see id.), the meaning of "non-promotional" is unclear.

[35] See Bass et al., Surveys of Medical Liaison Practices Across the Pharmaceutical Industry: A Review, 43 Drug Info. J. 685, 686 (2009).

[36] Id.

sites, educating investigators, attending investigator meetings, and responding to unsolicited requests.[37]

FDA has repeatedly recognized the value that these professionals add to the communication of medical and scientific information; the Agency has, for example, required the use of MSLs to fulfill communication and physician training requirements associated with various products' Risk Evaluation and Mitigation Strategies (REMS). FDA has indicated that MSLs may communicate off-label information in certain contexts (e.g., to share risk information in connection with REMS requirements, to respond to questions about off-label use data[38]), but it has never addressed more broadly the ability of MSLs to affirmatively communicate off-label information about their products. We ask the Agency to clarify that MSLs may share truthful and nonmisleading off-label information and that this activity constitutes scientific exchange.

3. Pipeline Information

Drug and device manufacturers must occasionally affirmatively communicate regarding their research and development efforts, commonly referred to as the product "pipeline." Pipeline discussions are critical to industry operations, as they not only spur investment in new projects, but also are fundamental to aid the research collaborations often necessary to ensure a successful clinical development program. The information, which may be directed to potential investors or clinical investigators, clinicians, researchers, and insurers (including government payers), may take various forms, but often includes references to specific product candidates and investigational uses of marketed products. Whether posted on company websites, discussed at conferences, or communicated through other fora, these pipeline presentations represent scientific exchange in its most classic form because they focus on the dissemination of data regarding development-stage products. We therefore request that FDA explicitly permit manufacturers to engage in pipeline discussions provided that the scientific exchange criteria are otherwise satisfied.

4. Investigator-Initiated Research Websites

Medical product manufacturers frequently provide grant monies for or products to be used in investigator-initiated research (IIR) that advances medical or scientific knowledge about the manufacturers' products. Aside from this limited support from the company, investigators assume responsibility for all aspects of their research, including protocol development, institutional and regulatory approval, study conduct,

[37] See, e.g., Morgan et al., History and Evolution of Field-Based Medical Programs, 34 Drug Info. J. 1049, 1051 (2000); see also id. at 687 (noting that MSLs meet an "unmet medical information need").
[38] See FDA, Draft Guidance on Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices, at 5 (Dec. 2011).

data analysis, and communication of results.[39] To facilitate IIR, manufacturers may sponsor websites or host online portals that allow potential investigators to learn more about the company's research interests and the criteria for collaboration, as well as permit the submission of clinical trial protocols and grant applications for the company's review. Similar to the pipeline presentations discussed above, these IIR websites may contain information about new uses of marketed products as well as information about investigational products. While allegations of off-label promotion arising from sponsorship of IIR have been made by DOJ in the past,[40] FDA has never (to our knowledge) commented on manufacturer communication about IIR. We ask that the Agency recognize that manufacturers are permitted to engage in IIR discussions and to sponsor IIR websites so long as the information satisfies the criteria for scientific exchange as set forth above.

5. Rebuttal of Comparative Effectiveness Research Findings

Comparative effectiveness research (CER) purportedly aims to support clinical decision-making by providing recommendations on which products are safe, efficacious, and cost-effective.[41] Although CER has long been conducted and distributed by public health agencies and private health plans, it promises to gain even more prominence as a result of the creation of the Patient Centered Outcomes and Research Institute (PCORI), which was established in 2010 and has a mandate that includes the sponsorship and assessment of CER.[42] Through publication of the research findings, for example, so-called "academic detailing,"[43] a variety of information may be disseminated about a manufacturer's products by AHRQ and other government entities. Such information often includes analyses of products for unlabeled uses, and the findings may be based on observational studies, meta-analyses, or other information that may not constitute the "substantial evidence" typically required in the

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[39] See, e.g., FDA, Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs), available at http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm071098.htm (describing sponsor responsibilities and making clear that companies that provide study drug are not study sponsors).

[40] See DOJ, Press Release: Pharmaceutical Giant AstraZeneca to Pay $520 Million for Off-Label Drug Marketing (Apr. 27, 2010), available at http://www.justice.gov/opa/pr/2010/April/10-civ-487.html (alleging among other things that the company "engaged doctors . . . to conduct studies on unapproved uses of Seroquel").

[41] See, e.g., Institute of Medicine, Initial Priorities for Comparative Effectiveness Research, at 29 (2009).

[42] See PCORI Mission Statement, available at http://www.pcori.org/about/mission-statement-2/ (explaining that PCORI's aims include "producing and promoting" CER).

[43] It is expected that PCORI's findings will be shared with clinicians and payers through in-person visits and publicity campaigns by the Agency for Healthcare Research and Quality (AHRQ), which has awarded multi-million dollar contracts to various companies for that purpose. See Joshua D. Lenchus, A Federal Unsales Force?: "Academic Detailing" on Medical Treatments and the Oversight Imperative, The Washington Legal Foundation Legal Backgrounder (Apr. 22, 2011), available at http://www.cohealthcom.org/wp-content/uploads/2011/07/click-here.pdf.

prescription drug context for comparative claims. What results is an asymmetrical scheme in which CER findings may be publicized without restriction by government entities, payers, or others, while manufacturers may not even respond to CER findings without risking government allegations of unlawful "promotion."[44] To the extent that manufacturers want to rebut CER (e.g., when it is based on faulty assumptions or methodological errors), the uncertainty in the regulatory scheme prevents them from doing so.

An FDA official recently stated that a manufacturer may "correct" or "dispute" a CER finding by a payer, researcher, or governmental entity,[45] but the contours of that position have not been clarified, nor has the position been adopted by in a binding manner by the Agency. The FDA official emphasized, moreover, that the manufacturer's response to CER may be appropriate only to the extent that it was "non-promotional" and consistent with the product labeling. Not only is there no way to determine what "non-promotional" means in this setting, but also for off-label CER in particular, manufacturers are left apparently unable to rebut CER findings, no matter how inaccurate. In recognition of the value of CER and the importance of the flow of truthful scientific information,[46] we ask that FDA explicitly recognize that manufacturers are entitled to respond to CER statements made by third parties, whether or not off-label, provided that the discussions comply with the scientific exchange parameters described above.

[44] See Scott Gottlieb & Coleen Klasmeier, Comparative Effectiveness Research: The Need for a Uniform Standard, AEI Outlook (June 2009), available at http://www.aei.org/files/2009/06/09/06%20HPO%20Gottlieb-g.pdf.

[45] See Gregory Twachtman, FDA Product Promotion Regs Shouldn't Stop Companies from Challenging CER Results, Official Says, The Pink Sheet (Feb. 10, 2012) (describing a presentation made by Bob Temple, Deputy Center Director for Clinical Science in FDA's Center for Drug Evaluation and Research, at the National Pharmaceutical Council conference on "Asymmetry in the Ability to Communicate CER Findings: Ethics and Issues for Informed Decision Making").

[46] As discussed above, manufacturers are superior repositories of information about their products and are thus uniquely positioned to communicate about them.