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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This petition is submitted on behalf of seven medical product manufacturers[1] pursuant to 21 C.F.R. § 10.30 to ask the Commissioner of Food and Drugs to clarify FDA regulations and policies with respect to manufacturer dissemination of information relating to new uses of marketed drugs and medical devices.

I. ACTIONS REQUESTED

We request that the Commissioner clarify FDA regulations and policies governing certain communications and activities relating to new uses of marketed products. The specific actions requested are discussed further below.

II. STATEMENT OF GROUNDS

A. THE PUBLIC HEALTH CONTEXT

FDA is the expert federal agency designated by Congress to assure the safety, effectiveness, and proper labeling of new drugs and medical devices. According to FDA's statutory mission statement, which was added to the FDCA in 1997:

> [FDA] shall—
> (1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;
> (2) with respect to such products, protect the public health by ensuring that—
> . . . (B) human and veterinary drugs are safe and effective;

[1] This petition is submitted on behalf of the following companies: Allergan, Inc.; Eli Lilly and Company; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Novo Nordisk, Inc.; Pfizer, Inc.; and sanofi-aventis U.S. LLC.

(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;

. . .

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with . . . manufacturers, . . . of regulated products.

21 U.S.C. § 393. As this provision emphasizes, FDA must not only safeguard the public health by managing the risks of medical product use, but also promote the health of the public by facilitating the appropriate availability of new drugs and medical devices. The agency must perform these functions through appropriate expert consultation and cooperation with important stakeholders, including specifically drug and medical device manufacturers.

Consistent with FDA's mission statement, a cornerstone of the agency's activities is the review of new drugs and medical devices before marketing in accordance with the new drug and medical device clearance and approval provisions of the FDCA. Under those provisions, subject to certain limited exceptions, careful premarket review is required before a manufacturer is legally entitled to introduce onto the United States market any "new drug" or any medical device. Once a drug or medical device has been authorized for marketing, it must be accompanied by labeling containing information adequate for the safe and effective use of the product. 21 C.F.R. §§ 201.100(c), 801.109(c).

Such labeling is not intended to be, and indeed cannot be, comprehensive. In developing a new medical product, the manufacturer in the first instance determines the use for which the product will be investigated, in the laboratory and then in human subjects through clinical trials. See, e.g., 21 C.F.R. pts. 312, 812 (describing regulatory procedures for clinical trials of new drugs and medical devices). Decisions relating to the use under investigation reflect a variety of considerations, including the likelihood that the product has an appropriate risk/benefit profile for that use, the unmet medical need for the product for that use, and the feasibility of designing and completing clinical trials of the product for that use. If the product is ultimately authorized for marketing by FDA, its labeling contains a summary of the essential scientific information relating to the investigated use(s) of the product. Uses not set forth in labeling are often referred to as "new" or "off-label" uses.[2]

[2] "The uses that are approved by the agency are sometimes referred to as 'labeled' uses because they appear in the product's approved or cleared labeling. Uses that do not appear in the labeling and are not approved by the agency are referred to as 'unapproved,' 'unlabeled,' 'off-label,' or 'extra-label' uses." Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices: Request for Comments, 59 Fed. Reg. 59,820, 59,820 n.1 (Nov. 18, 1994).

Off-label use is lawful, and it is axiomatic that physicians may prescribe both drugs and devices for uses not included in the product labeling.[3] In addition to being lawful, off-label prescribing is "common, can be a source of innovation, and in some settings may represent the standard of care."[4] For many diseases, off-label uses are the only therapies available,[5] and for others, "a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease."[6] Indeed, as the American Medical Association (AMA) has noted, "[u]p to date, clinically appropriate medical practice at times requires the use of pharmaceuticals for 'off-label' indications."[7]

Congress has recognized that off-label uses are appropriate for quality patient care; in a number of situations, it has mandated that payors in federal health care programs must provide reimbursement for off-label uses that are "medically accepted" and may reimburse for other off-label treatments. E.g., 42 U.S.C. §§ 1396r-8(d)(1)(B)(i), (k)(6), (g)(1)(B)(i).

The public health necessity of off-label use has also long been recognized by FDA.[8] Accordingly, the agency has emphasized the value of physicians having as

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[3] See 21 U.S.C. § 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."); 21 C.F.R. § 312.2(d) (exemption from FDA regulations for "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by the agency); Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,733 (June 9, 1983) ("Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling."); Legal Status of Approved Labeling for Prescription Drugs, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972) ("[T]he physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.").

[4] Donna T. Chen et al., U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey, 18 Pharmacoepidemiology & Drug Safety 1094 (2009) (footnotes omitted).

[5] See Bryan A. Liang and Tim Mackey, Reforming Off-Label Promotion to Enhance Orphan Disease Treatment, Science (Jan. 15, 2010), at 3.

[6] Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. on Government Reform and Oversight, 104th Cong. 12 (1996) (statement of Sarah F. Jaggar, Dir. of Health Services Quality and Public Health Issues, Health, Education, and Human Services Division, GAO). Off-label use has particular importance in the oncology field, where doctors depend on off-label uses because they "are regularly faced with few approved treatment options, especially if the first treatment didn't work." See Am. Cancer Soc., Off-Label Drug Use, http://tinyurl.com/ygxobso (last visited June 22, 2011). Indeed, the National Comprehensive Cancer Network estimated in 2005 that "50% to 75% of all uses of drugs and biologics in cancer care in the United States are off-label." Michael Soares, Off-Label Indications for Oncology Drug Use and Drug Compendia: History and Current Status, 1 J. of Oncology Prac. 102, 104 (2005).

[7] Memorandum of the AMA House of Delegates, Resolution 820, Off-Label Use of Pharmaceuticals (Sept. 21, 2005), available at http://tinyurl.com/yfpwmyo (emphasis added).

[8] In 1998, FDA provided guidance to institutional review boards regarding off-label use, stating that "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement [sic]." FDA, "Off-Label"

much truthful, accurate, and non-misleading new use information as possible, noting the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products."[9] The dissemination of up-to-date medical information about a product—irrespective of the product's labeled indications—helps to guide physicians in their treatment decisions and ensures that patients receive care based on current, sound, scientific and clinical information.[10] Manufacturers are uniquely positioned to provide such information,[11] and as a result, the agency's policy is to seek a "balance" between two objectives: limiting off-label "promotion" on the one hand, while allowing manufacturer communication of reliable scientific information regarding off-label uses on the other.[12]

B. THE NEED FOR CLEARER REGULATION

FDA has repeatedly opined on the importance of off-label use and manufacturer dissemination of information relating to such use, and indeed, has

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and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet, available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (emphasis added). More recent guidance from FDA states that "off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care." FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved or Cleared Medical Devices (Jan. 2009), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm. In certain drug shortage situations, FDA has even gone so far as to recommend to physicians that they use a substitute drug product off-label until the shortage has been resolved. See, e.g., FDA, Current Drug Shortages, www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm (last visited June 22, 2011) (describing current drug shortages and referring to alternatives, including off-label uses).

[9] See Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998) (emphasis added).

[10] The Associate Commissioner for Health Affairs at FDA wrote in 1992 that "the very latest information that can be of value to physicians . . . . must be made available as soon as possible. Frequently, unlabeled use information is extremely important." Stuart Nightingale, Unlabeled Uses of Approved Drugs, 26 Drug Info. J. 141, 145 (1992). See also Donna T. Chen et al., U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey, 18 Pharmacoepidemiology & Drug Safety 1094 (2009) (concluding that survey results point out "a pressing need for more effective methods to inform physicians about the evidence base, or lack thereof, for drugs they prescribe off label").

[11] For example, FDA has recognized that "[s]cientific departments within regulated companies generally maintain a large body of information on their products," Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices: Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994). This information relates to the risks, optimization strategies, and rewards of off-label uses and can help guide practitioners' decisions. See also 1997 Annual Meeting of the American Medical Association, supra; see also More Information for Better Patient Care: Hearing of the Senate Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of Dr. Gregory H. Reaman, Dir., Medical Specialty Services, Children's National Medical Center) ("Pharmaceutical and biotechnology companies obviously have an interest in supporting new uses of their products, but they also happen to be in the best position to share information with the physician community at the earliest possible time, when it may really make a difference in treatment options.").

[12] 59 Fed. Reg. at 59,823; see also Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996); Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56,412, 56,412 (Nov. 27, 1992).

explicitly recognized important mechanisms for the sharing of truthful and non-misleading scientific information.[13] While the agency has made clear that these mechanisms exist, there is a significant lack of clarity as to the practices they permit. Further complicating matters, FDA policies may be difficult to interpret due to the use of ambiguous language and undefined terms like "promotion" and "scientific exchange." Moreover, manufacturers have often pieced together the agency's positions over time from Federal Register documents, guidance, letters, and similar pronouncements. But these pronouncements are not only difficult to find, but also often nonbinding. This void creates significant obstacles for the stakeholders that must rely on FDA's legal interpretations.

The lack of clarity and vagueness surrounding the contours of permissible manufacturer speech has significant consequences to manufacturers, the government, physicians, and patients. Companies dedicate substantial resources to compliance, with many of them staffing entire departments for this purpose and engaging outside counsel solely to advise on compliance-related matters. The paucity of clear rules requires manufacturers, their lawyers, and prosecutors to infer operative law from FDA's letters and other agency materials, as well as the publicly available papers in settled criminal investigations, such as government press releases, informations, statements of factual bases for pleas, and related documents. Once manufacturers have discerned what they believe is the correct interpretation, they develop internal guidelines and policies governing the dissemination of off-label information and train their sales representatives, field medical personnel, and other relevant employees on the information that may appropriately be shared about their products. In the face of uncertainty, manufacturers may develop policies that do not align with the government's expectations. As a result, each individual manufacturer may either over- or under-communicate clinically relevant information, with significant attendant consequences for the public health.[14]

C. REQUESTED ACTIONS

We set forth below the publicly available sources of information embodying certain of FDA's policies on the dissemination of information on off-label uses. We request that FDA affirm and clarify the contours of these policies in regulations that are legally binding[15] and believe that the agency could offer comprehensive guidance consistent with its mission to protect the public health.

1. Manufacturer Responses to Unsolicited Requests

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[13] See, e.g., the establishment of mechanisms for sharing off-label information in the context of scientific exchange and in response to an unsolicited request, discussed infra Part II.C.1-2.

[14] This petition is limited to the regulatory standards that govern the speech of medical product manufacturers. Important constitutional concerns arise out of the regulatory scheme. See Sorrell v. IMS Health, Inc., No. 10-779, __ S. Ct. __ (decided June 23, 2011); Reno v. American Civil Liberties Union, 521 U.S. 844, 871-72 (1997) (vagueness presents "special concern" when it has a "chilling effect on free speech" as well as where citizens are put at risk of criminal prosecution).

[15] We strongly prefer changes to FDA's regulations rather than guidance documents.

We have long understood that manufacturers may provide new use information in response to unsolicited requests, but no law or regulation states this rule or defines the boundaries of the safe harbor. Since 1982, FDA has expressly recognized the permissibility of manufacturers' communications about off-label uses in response to "any and all unsolicited requests received from outside the company for information about a drug manufactured, distributed or repacked by the company." The Division of Drug Advertising and Labeling (DDAL), the Division of Drug Marketing, Advertising, and Communications' (DDMAC's) predecessor entity, set forth this policy in a one-page document intended to provide "clarification and guidance" to industry.[16] The document explained that such responses did not constitute "labeling," but were rather "personal communication[s] between the requester and firm" under the FDCA. DDAL maintained that the exception only applied if a company did not expressly encourage the request, and recommended including the package insert in company responses. DDAL also said it would "reconsider" the policy if "problems or abuses [were] noted."

In 1994, DDMAC reiterated the unsolicited requests policy in a document entitled "Current Issues and Procedures," stating that "individual, nonpromotional responses by pharmaceutical companies to specific, unsolicited requests for information will not be considered as promotional labeling."[17] The restated policy withdrew the recommendation that responses include references to the indications and package insert. It also added two new criteria, that companies: (1) "maintain documentation concerning the nature of the request(s)," and (2) avoid a "pattern of repeated dissemination of materials." DDMAC explained that merely preparing material for routine dissemination could qualify as solicitation.

That same year, FDA articulated a further revised version of the policy in a notice published in the Federal Register. Acknowledging the "large body" of scientific information available within companies, the notice established that, "[w]hen health care professionals request such information, companies can provide responsive, non-promotional, balanced scientific information, which may include information on unapproved uses, without subjecting their products to regulation."[18] The notice did not identify conduct that could constitute solicitation, and it implied that responses would not subject a company's drug to any kind of regulation. Unlike preceding statements, FDA's notice left open the possibility that corporate employees other than members of a medical affairs department could issue responses. Finally, the notice was for the first time officially binding on FDA, 21 C.F.R. § 10.85(d)(1), and by its terms covered not only drug products but also medical devices.

The passage of the Food and Drug Administration Modernization Act (FDAMA) of 1997 changed little about FDA's policy on responses to unsolicited requests. FDAMA, in Section 401, stated that any prohibition on off-label promotion

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[16] See DDAL, Position on the Concept of Solicited and Unsolicited Requests (Apr. 22, 1982).
[17] DDMAC, "Current Issues and Procedures" (Apr. 1994).
[18] Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices: Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

should not "be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner." FDA affirmed this principle in subsequent regulations, which were codified in 21 C.F.R. part 99.[19]

The expiration of FDAMA Section 401 in 2006 led the agency to issue a draft guidance document on the distribution of reprints of journal articles and reference publications discussing off-label uses.[20] The reprints guidance made clear that responses to unsolicited requests were governed by FDA's 1994 Federal Register notice, discussed above. The reprints guidance also cited FDA's 1997 Guidance on Industry-Supported Scientific and Educational Activities, in connection with which FDA stated with respect to unsolicited requests: (1) manufacturers could provide "technical support" (e.g., "preparing slides or audiovisual materials") for a scientific or educational activity in response to an unsolicited request; and (2) whether a statement made in the context of a scientific or educational activity qualified as "promotional"—a relevant factor under the 1994 FDA statement on responses to unsolicited requests—could depend on whether it had been disseminated after an initial program.[21] Although the draft guidance confirmed that there is an "unsolicited requests" safe harbor, it did not codify that rule or adequately define its scope.

On behalf of the medical product manufacturers we represent, we ask FDA to promulgate binding regulations embodying FDA's current policy on responses to unsolicited requests. To assure that the policy affords manufacturers a meaningful "safe harbor" and therefore fulfills FDA's objective of attaining a "balance" between prohibiting off-label promotion and allowing appropriate dissemination of information relating to off-label uses, FDA should also clearly distinguish a non-promotional response to an unsolicited request from product promotion[22] and clarify that responses to unsolicited requests are excluded from the scope of materials that can create an intended use under 21 C.F.R. §§ 201.128 and 801.4 and do not constitute "advertising" or "labeling."

2. "Scientific Exchange"

We have also long understood that manufacturers may engage in "scientific exchange," but no law or regulation adequately defines the boundaries of "scientific exchange." This important and well-accepted concept is only mentioned in a regulation in the narrow context of 21 C.F.R. § 312.7, which prohibits a drug

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[19] See Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556, 64,558 (Nov. 20, 1998) (formerly codified at 21 C.F.R. § 99.1(b)).

[20] Draft Guidance for Industry on 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, 73 Fed. Reg. 9,342 (Feb. 20, 2008).

[21] Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,091 (Dec. 3, 1997).

[22] FDA has stated that speech about an off-label use creates an "intended use" if it "expressly or implicitly promote[s]" the safety or efficacy of that use, but that a manufacturer may disseminate non-promotional information without triggering penalties. See Decl. of Dr. Robert Temple ¶ 10, Allergan v. United States, No. 09-1879 (D.D.C. Dec. 11, 2009). But this definition does not provide adequate guidance as to what would constitute "implicit[]" promotion of safety or efficacy.

manufacturer from representing in a promotional manner that an investigational new drug is safe or effective. In recognition of the critical importance of scientific exchange in the advancement of medicine, FDA made sure to carve out an exception from this otherwise restrictive regulation for scientific exchange. The scientific exchange safe harbor, which FDA has repeatedly affirmed in various rulemaking and guidance development proceedings over the years, suggests that the agency was both cognizant of the First Amendment concerns attendant to § 312.7 and careful to limit the scope of the regulatory prohibition. Nonetheless, the agency has not issued a comprehensive, binding statement as to the contours of the safe harbor. There is also no regulation confirming that a similar safe harbor applies to "scientific exchange" about investigational medical devices.

Drugs. FDA's regulations governing investigational new drugs, 21 C.F.R. pt. 312, provide that the regulatory prohibition on the promotion of an investigational new drug as safe or effective should not be construed to prohibit "scientific exchange." The "scientific exchange" language dates back to 1963, when FDA first published the investigational new drug regulations following enactment of the Drug Amendments of 1962.[23]

Amendments to the "scientific exchange" rule were published on March 19, 1983.[24] These amendments "retain[ed], essentially unchanged, the current provisions prohibiting promotion and commercialization of investigational drugs."[25] On May 22, 1987, FDA published a separate final rule providing procedures under which investigational new drugs could be made available to "desperately ill patients" prior to general marketing.[26] In the preamble to that rule, FDA indicated that, to qualify as "scientific exchange," statements must: (1) make clear that a drug is investigational; (2) make no claims that a drug has been proven to be safe or effective; and (3) be truthful and non-misleading when measured against available information on the drug. Id. at 19,475. FDA also referred to several examples of permissible scientific exchange: "publishing results of scientific studies, letters to the editor in defense of public challenges, investigator conferences." Id.

Medical Devices. In 1976, FDA proposed regulations prohibiting the promotion of investigational devices.[27] FDA finalized only the part of its proposal relating to intraocular lenses (IOLs).[28] For a time, this provision, codified at 21 C.F.R. § 813.50(a), expressly did "not restrict the full exchange of scientific information concerning" a device, "including dissemination of scientific findings." In 1997, FDA

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[23] Procedural and Interpretative Regulations: Investigational Use, 28 Fed. Reg. 179 180 (Jan. 8, 1963).
[24] New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 8,798, 8,833 (Mar. 19, 1987).
[25] Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,734 (June 9, 1983).
[26] See Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 19,466 (May 22, 1987).
[27] Proposed Investigational Device Exemptions, 41 Fed. Reg. 35,282 (Aug. 20, 1976).
[28] See Investigational Device Exemption Requirements, 42 Fed. Reg. 58,874 (Nov. 11, 1977).

issued a final rule that removed and reserved 21 C.F.R. part 813, effective March 31, 1997.[29]

In a separate proposed rule in 1977, FDA affirmed manufacturers' entitlement to engage in scientific exchange.[30] Instead of issuing a final rule, however, FDA published a guideline on monitoring.[31]

Throughout the following decade, CDRH continued to recognize "scientific exchange" relating to medical devices. CDRH alluded to scientific exchange in a series of warning letters issued in the 1990s, stating in each letter: "Although FDA does encourage the full exchange of scientific information concerning investigational devices, including dissemination of scientific findings through scientific/medical publications or conferences, safety and efficacy conclusions and statements of a promotional nature are inappropriate." A guidance document published in 1999 did not clarify the scope of permissible scientific exchange for devices, although it did make clear that manufacturers could "make known through a notice, publication, display, mailing, exhibit, announcement, or oral presentation the availability of an investigational device for the purpose of obtaining clinical investigators to participate in a clinical study involving human subjects."[32]

We ask FDA to clarify its position on scientific exchange as set forth in the 1987 Federal Register notice and to bring appropriate parity to the rules for drugs and medical devices. Specifically, FDA should state that, in its view, to qualify as "scientific exchange," statements must: (1) make clear that a use or product is not FDA-approved or -cleared; (2) make no claims that a use or product has been proven to be safe or effective; and (3) be truthful and non-misleading when measured against available information on the use or product.

Because there is no principled reason to distinguish drugs from medical devices in this context, and FDA has in the past affirmed that scientific exchange is permissible for medical devices as well as drugs, we further request that FDA amend 21 C.F.R. § 812.7 to include analogous "scientific exchange" language, and to affirm that the principles in the 1987 Federal Register notice apply equally to medical devices. In addition, we ask that FDA promulgate regulations expressly providing that the "scientific exchange" concept applies not only with respect to investigational new drugs and medical devices, but also with respect to new uses of already approved drugs and medical devices.

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[29] Investigational Device Exemptions, 62 Fed. Reg. 4,164 (Jan. 29, 1997).
[30] Proposed Establishment of Regulations, 42 Fed. Reg. 49,612 (Sep. 27, 1977) (proposed 21 C.F.R. § 52.118).
[31] See Monitoring of Clinical Investigations, 53 Fed. Reg. 4,723 (Feb. 17, 1988).
[32] FDA, Guidance for Industry and FDA Staff on Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects (Mar. 19, 1999), at 1, available at www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073585.pdf.

Finally, FDA should clarify that activities meeting the definition of scientific exchange are excluded from and cannot be used to establish an "intended use" within the meaning of 21 C.F.R. §§ 201.128 and 801.4. FDA also should clarify that activities meeting the definition of scientific exchange do not constitute "labeling" or "advertising."

3. Interactions with Formulary Committees, Payors, and Similar Entities

We have also long understood that manufacturers may engage in communications with formulary committees, payors, and similar entities regarding investigational products or off-label uses, but again the boundaries of permitted communications are unclear. Manufacturers must be able to provide (and often do provide) information to formulary committees, managed care organizations, and other third-party payors in order to obtain coverage of and reimbursement for their products. DDMAC has expressed the view that certain of these communications are within its regulatory jurisdiction and are generally expected to be on-label.[33] In order to ensure that an investigational product will be reimbursable immediately upon approval and launch, or that an off-label use is reimbursable, however, manufacturers may be interested in communicating information about off-label uses or investigational products pre-approval. Manufacturers may also be interested in communicating information concerning off-label uses of approved or cleared products to payors to address prior authorization or other utilization control issues.

We understand that FDA representatives have, in the past, worked with the Academy of Managed Care Pharmacy (AMCP)—a national professional organization for individual pharmacists, health care practitioners (non-pharmacists), and associates who practice in managed care settings—to develop a standard format for healthcare systems to use in asking drug manufacturers to submit comprehensive product information (including on- and off-label use information) to assist in coverage decisions. Unfortunately, FDA itself has not publicly stated that submissions of drug information that follow the AMCP format and are either submitted in response to an unsolicited request from a healthcare system or consistent with the principles of scientific exchange would be regarded by the agency as permissible. Moreover, nothing akin to the AMCP format exists specifically for medical devices, and the relevance of the AMCP approach to devices remains unclear.

As a result, the extent to which manufacturers can provide safety, efficacy, and health care economic information concerning pre-approval products or unapproved uses of approved products requires clarification. We briefly describe our understanding of these issues below.

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[33] See, e.g., DDMAC, "Current Issues and Procedures," supra (stating that formulary kits and similar materials, such as those prepared for review by formulary committees, that discuss a regulated product and that are prepared for and disseminated to hospitals or managed care organizations constitute promotional labeling).

Communications Regarding Investigational Products or Off-Label Uses of Approved or Cleared Products Generally. FDA's regulations prohibit manufacturers from commercializing investigational medical products, 21 C.F.R. §§ 312.7(a) & 812.7, or otherwise representing "in a promotional context that an investigational new [product] is safe or effective for the purposes for which it is under investigation or otherwise promote the [product]." 21 C.F.R. § 312.7(a).

Although one intent of §§ 312.7 and 812.7 is to restrict manufacturers from making claims of safety or effectiveness regarding investigational products, the former provision is explicitly not intended to restrict "the full exchange of scientific information" concerning the investigational drug. Thus, we believe that communications to payors that focus on an investigational new drug are permissible so long as they do not commercialize the product and are made in the context of scientific exchange. We also believe that the same "scientific exchange" concept applies to investigational devices and off-label uses of previously approved drugs and devices. Unfortunately, as discussed above, FDA has not adequately explained what is meant by the terms "commercialization" or "exchange of scientific information," and no regulation explicitly states that "scientific exchange" is permitted for investigational devices or off-label uses.

Communication of Health Care Economic Data Concerning Unapproved Products or Unapproved Uses of Approved Products. The FDCA allows manufacturers to provide to payors "health care economic information" that "directly relates" to an approved indication, so long as the information is based on "competent and reliable scientific evidence." 21 U.S.C. § 352(a). Because Congress specifically limited communication of health care economic information to labeled uses, it could be inferred that communication of health care economic information about off-label uses would not be permitted in labeling, except in the context of scientific exchange or in response to an unsolicited request. FDA has not addressed this issue specifically, however.

To address the uncertainties highlighted above, we respectfully request that FDA address whether, and to what extent, health care economic and other product-related information may be shared with payors. Specifically, we recommend that FDA indicate that communication of truthful, non-misleading information by or on behalf of a manufacturer to payors, whether prior to or after approval or clearance of the manufacturer's product, will be considered scientific exchange when such communication is: (1) delivered by representatives of the manufacturer with appropriate medical, scientific, or health care economic or health outcomes expertise; (2) provided to payors who are carrying out their responsibilities for the selection of products and coverage of therapies and products for managed care or other similar organizations; and (3) limited to (a) health care economic information directly related to the indication for which the product is expected to be approved or cleared or (b) published scientific or health care economic information.

4. Dissemination of Third-Party Clinical Practice Guidelines

Leading associations of medical professionals, academic institutions, and government agencies often produce clinical practice guidelines, which are meant to

guide decisions concerning diagnosis, management, and treatment in specific areas of health care. Such clinical guidelines are most often based on a thorough examination of the most robust and most up-to-date evidence and data. The primary objective of such guidelines is to raise the quality of care and to optimize clinical outcomes. The recommended use of any particular drug or medical device in a clinical practice guideline may, however, vary from the approved or cleared labeling for that product (e.g., the guidelines may recommend an off-label use of the product). The tension between these concepts—dissemination of recognized practice guidelines to improve patient care and the prohibition on promotion of a product for off-label uses—is evident; what is less evident, however, is whether, or to what extent, a manufacturer can disseminate such guidelines.

There are no formal FDA policies specifically relating to manufacturer dissemination of clinical guidelines that may discuss off-label uses. We propose that FDA confirm the following: A manufacturer may disseminate clinical guidelines if they are: (1) developed or adopted by a nationally or internationally recognized scientific or medical organization or by a federal or state government agency, or are recognized by the National Guideline Clearinghouse or the National Quality Measures Clearinghouse; (2) reproduced in a manner that retains the same format, content, and configuration of the guidelines as published by the organization or agency with respect to all indications or categories for which the manufacturer's product is recommended; (3) reproduced by the manufacturer to include all guidelines or measures relating to products that have the same indication as the indication for which the manufacturer's product is recommended; and (4) accompanied by relevant disclaimers and disclosures.

D. CONCLUSION

The confusion surrounding the issues discussed above results in significant difficulties for companies in their day-to-day decision-making. Most companies, including the manufacturers on whose behalf we submit this petition, dedicate substantial time and resources to ensuring that their business practices are compliant with FDA rules and regulations. They rely heavily on FDA's statutory interpretations to guide them.

Unfortunately, the current state of regulatory guidance is not clear or comprehensive, or in some cases, even binding. That lack of clarity places manufacturers at risk of criminal and civil sanctions if they cannot correctly guess where the government would draw a line in the matters detailed above. Industry should not have to refer to the terms of DOJ settlements or informal statements of FDA officials to learn what is expected of them prospectively. FDA can, and should, take up its responsibility to interpret the FDCA with respect to the dissemination of new use information. We therefore urge FDA to establish comprehensive, clear and binding regulations to guide the industry in the critical matters discussed herein.

III. OTHER REQUIRED INFORMATION FOR FILING OF CITIZEN PETITION

A. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

B. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

C. CERTIFICATION

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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