December 16, 2011

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

Re: FDA-2011-P-0512-0001/CP

To Whom It May Concern:

EMD Serono, Inc., pursuant to 21 C.F.R. § 10.30(d), respectfully submits these comments to the Citizen Petition submitted on July 5, 2011, Docket # FDA-2011-P-0512-0001/CP, on behalf of Allergan, Inc., Eli Lilly and Company, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Pfizer, Inc., and sanofi-aventis U.S. LLC (the “Citizen Petition”). As outlined herein, EMD Serono supports the Citizen Petition and joins these companies in requesting FDA to codify its policies governing manufacturer dissemination of truthful, nonmisleading information about FDA-approved products. Our submission focuses on one aspect of the petition, related to interactions with formulary committees, payors, and similar entities (collectively, “payors”), and requests FDA to clarify that manufacturers may (1) publish and disseminate health care economic information in certain peer-reviewed journals; (2) present health care economic information at managed care and other payor conferences; and (3) disseminate health outcomes research to payors and similar entities. The parameters of these requests are discussed in detail below.

I. Background

EMD Serono is a leader in the U.S. biopharmaceutical industry, with FDA-approved therapies for relapsing forms of Multiple Sclerosis, infertility, and metabolic endocrinology. Like the manufacturers on whose behalf the Citizen Petition was filed, EMD Serono maintains a vast body of information about its products ranging from registration-quality clinical trial data, to robust post-marketing information, to case studies and anecdotal evidence. We support the Citizen Petition and agree with its primary point—namely, that the contours of permitted practices are poorly defined with regard to the dissemination of information relating to investigational products and uses. As such, EMD Serono joins the seven manufacturers in their request that FDA clarify and codify its policies regarding manufacturer communication of off-label information.

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The Citizen Petition emphasizes the importance of manufacturer communication with payors and underscores the lack of FDA regulation or guidance governing this behavior. Specifically, the Petition highlights the uncertainty regarding permissible communications about investigational products and uses, both generally and in the context of health care economic data. Although not explicitly addressed in the Citizen Petition, there is a similar lack of clarity with respect to on-label communication with payors. Below, we describe the gaps in FDA regulation and guidance and request that the agency outline the activities a manufacturer may pursue when providing payors with information about on-label uses of its products.

1. Interactions with Payors

In addition to routine communication with health care providers and consumers about its products, EMD Serono, like other manufacturers, also provides product information to payors that utilize it to design programs and policies for health care enrollees. Much of this communication with payors is proactive: EMD Serono, for example, regularly shares new information about the health benefits associated with use of its products. Occasionally, Serono and other manufacturers provide product information to payors in response to unsolicited requests. In either case, the primary purpose is to ensure that payors have access to reliable, up-to-date product information on which to base coverage decisions.

Consistent with an increased focus on comparative effectiveness research and driven in part by rising health care costs, payors have expected more information from manufacturers in recent years. In addition to safety and effectiveness data, manufacturers' submissions to payors, as exemplified by the Academy of Managed Care Pharmacy Formulary for Format Submissions ("AMCP Format"), must now include varied sources of information that demonstrate the "economic value" of the product. Comparative effectiveness data "derived from studies including relevant populations, comparators, and outcomes . . . [is] expected for mature products," and pharmacoeconomic analyses, whether based on clinical trials with economic endpoints, economic modeling, or post-approval data collection, are now submitted by manufacturers for all products as a matter of course.

2. FDAMA Section 114

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1 See Letter from A. Bennett et al., to FDA, Docket # FDA-2011-P-0512-0001/CP (Jul. 5, 2011) [hereinafter the "Citizen Petition"], at 10.


3 See, e.g., AMCP Format (Oct. 2009), at 9 (describing the limitations of "traditional" forms of evidence such as clinical trials and post-marketing safety data in payor decision-making). The AMCP Format makes clear that manufacturer submissions should occur only in response to an unsolicited request from a health care system. Id. at viii.

4 Id.

5 Id. at Sections 4 & 5.
As discussed in the Citizen Petition, FDA has issued no regulations or guidance defining the scope of permissible payor interactions. The Division of Drug Marketing, Advertising, and Communications ("DDMAC") has stated informally that it considers these interactions to be within its regulatory jurisdiction and expects them to be on-label, but Section 114 of the Food and Drug Administration Modernization Act of 1997 ("FDAMA") contains the only explicit reference to communication between pharmaceutical manufacturers and payors. FDAMA Section 114 represented the culmination of a lengthy dialogue among FDA, manufacturers, payors, health care providers, and patients that focused on the use of pharmacoeconomic claims in product promotion. In 1995, DDMAC released draft principles for the review of pharmacoeconomic promotional claims and stipulated that such claims would be considered false and misleading unless substantiated by two adequate and well-controlled studies. That standard, while appropriate for promotional claims generally, was considered by industry, payors, and economists as too rigid for pharmacoeconomic claims. Specifically, commentators argued that adequate and well-controlled studies were expensive and time-consuming, thereby discouraging manufacturers from pursuing cost-effective analyses and creating the distinct possibility that economic data would be out-of-date by the time the clinical trial results were interpreted and reported. Additionally, there was a concern that experience obtained through controlled trials might deviate from actual use, as well as the general belief that truthful and nonmisleading pharmacoeconomic information could be obtained and subsequently conveyed in a more flexible manner.

FDAMA Section 114 permits manufacturers to provide promotional health care economic information ("HCEI") to a formulary committee or other similar entity in connection with the selection of prescription drugs for managed care organizations and similar organizations, provided that such information is "directly related to an approved indication" and "based on competent and reliable scientific evidence." In changing the evidentiary requirements for submissions to payors from "substantial evidence typically demonstrated by two adequate and well-controlled trials" to the "competent and reliable" standard, the provision gives pharmaceutical manufacturers more flexibility in promoting economic messages to managed care audiences. Discussions of the House and Senate prior to the provision's passage shed light on its purpose and the congressional rationale; adopting the new standard for pharmacoeconomic claims was meant to facilitate the communication of truthful, reliable, and timely health care economic information to payors, and limiting the provision's application to

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6 See Citizen Petition, at 10.
9 Pub. L. No. 105-115, 111 Stat. 2312 (codified at 21 U.S.C. § 352(a)). FDAMA Section 114 makes clear that such information will not be considered false and misleading or misbrand the product. The provision does not govern information shared in the context of scientific exchange (e.g., scientific, non-promotional data disseminated prior to FDA approval of a new use). See id.; see also Paul Radensky, Regulation of Pharmacoeconomics and Outcomes Research, Presented at the ISPOR 5th Annual International Meeting (May 24, 2000), at 13.
10 In drafting the provision, the Senate acknowledged the importance of HCEI and concluded that "[u]ndue restrictions on the ability of companies to make competent and reliable claims on the basis of cost, effectiveness, or
manufacturer communication with formulary committees and similar entities was designed to ensure that recipients of such information were qualified to interpret it.

FDAMA Section 114, while allowing important strides in the fields of cost-effective analyses and comparative effectiveness research, nevertheless left manufacturers unsure how to proceed in a practical sense. With the exception of “health care economic information,” none of the statutory terms are defined. As emphasized in the Citizen Petition,\(^\text{11}\) moreover, Congress did not clarify in the statute that the enumerated manufacturer activities were permitted to the exclusion of all others. Unfortunately, FDA has never released guidance on the interpretation of FDAMA Section 114, and manufacturers have no guidance whatsoever to instruct their interactions with payors.

The lack of FDA guidance regarding the permissible scope of such communications has raised questions about how information may be disseminated to payors. FDA has not made clear, for example, whether manufacturers may seek publication of HCEI in peer reviewed journals, whether they may present HCEI at managed care and other payor conferences, and whether manufacturers may disseminate related types of information—namely, health outcomes information—to payors under Section 114’s “competent and reliable scientific evidence.” Although EMD Serono believes that each of these practices is permissible under the law and consistent with First Amendment principles, we have proceeded with an abundance of caution, refraining from activities that may be permitted by law. We therefore join the manufacturers who filed the Citizen Petition to request the agency to codify its policies regarding interactions with formulary committees, payors, and similar entities and specifically address the following issues.

II. FDA Should Expressly Permit Manufacturers to Publish and Disseminate HCEI in Certain Peer-Reviewed Journals

Although FDAMA Section 114 expressly permits manufacturers, subject to the requirements outlined above, to provide HCEI directly to formulary committees, neither the statute nor FDA’s regulations and guidance explicitly address whether manufacturers may also submit such data to peer-reviewed journals and disseminate the resulting articles to formulary committees and similar entities. Publication of data that meets the statutory requirements of FDAMA Section 114, as discussed below, is desirable from a public health perspective and consistent with the law. To further the aims of the statute and to ensure that payors have the most reliable information available, EMD Serono urges FDA to expressly affirm that manufacturers may publish and disseminate truthful, nonmisleading HCEI in certain peer-reviewed journals without risk of enforcement action.

safety of approved uses of products interfere with the public health by encouraging the sale and use of needlessly expensive products.”

\(^{11}\) See Citizen Petition at 11.

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FDAMA Section 114 clearly permits manufacturers to share with payors HCEI that satisfies the statutory requirement, regardless of whether it has been published in a peer-reviewed journal. Because FDA has not stated so explicitly, and has never provided parameters with respect to how manufacturers may seek publication, however, EMD Serono is reluctant to publish HCEI for fear that the government could interpret it as an attempt to enlarge the audience with which this information may be shared. The company is concerned, moreover, that the government would evaluate the published HCEI not by the “competent and reliable” standard established in FDAMA Section 114, but rather by the heightened “substantial evidence” standard against which drug promotion is typically judged.

FDA’s lack of guidance in this area has profound effects on the quality of HCEI provided to managed care entities and other payors. Both the Federal Trade Commission (“FTC”) and FDA have repeatedly characterized the peer-review process as important to the integrity and reliability of information concerning approved drugs, as it helps to ensure that data is subject to rigorous review and untainted by allegations of manufacturer bias. Relevant guidance issued by FTC and FDA in the context of the substantiation of claims for dietary supplements—governed by the same “competent and reliable” standard on which FDAMA Section 114 was based—provides insight as to the value of peer-reviewed publications. The FTC has indicated that although publication of data in a scientific, peer-reviewed journal is not required to satisfy the “competent and reliable” standard, “the publication of a peer-reviewed study in a reputable journal indicates that the research has received some measure of scrutiny.”12 Similarly, FDA has stated that although publication in a peer-reviewed journal is not always necessary, it provides “some level of assurance that qualified experts have reviewed the research and found it to be of sufficient quality and validity to merit publication.”13

FDA’s Good Reprint Practices (the “Reprints Guidance”)14 offers the most relevant and direct endorsement of peer-review publication. There, FDA determined that the manufacturer dissemination of articles published in peer-reviewed journals—even if off-label—was appropriate provided that certain standards were met. The guidelines addressed considerations relating to the quality and independence of peer-review, the involvement of the manufacturer in editing the manuscript, the method of dissemination, and the weight of the evidence15 relied upon

15 Specifically, the Reprints Guidance requires the disseminated article to address “adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience.”
in the article. FDA repeatedly emphasized in the Reprints Guidance that the dissemination of truthful, nonmisleading information is critical to the public health, and the guidelines suggest that publication and ultimate dissemination of product information in a peer-reviewed journal is a permissible, non-promotional activity that remains so provided that certain safeguards are implemented.

As with the publication and dissemination of information related to unapproved uses, the publication and dissemination of HCEI in certain peer-reviewed journals should also be considered non-promotional and explicitly permitted in certain circumstances. Cognizant of Congress’s concern that HCEI distribution under FDAMA 114 be limited to payors and similar entities possessing the necessary expertise to evaluate it, we propose that FDA explicitly affirm that publication of HCEI in peer-reviewed journals such as the Journal of Managed Care Pharmacy and Value in Health, which are affiliated with reputable groups that focus on HCEI and other issues related to health care cost, quality, and outcomes, is appropriate. This approach would be consistent with Sorrell v. IMS Health, Inc., where the Supreme Court held that content- and speaker-based restrictions on commercial speech will fail heightened judicial scrutiny “in the ordinary case,” because it would allow publication of product-related communication regardless of the content (e.g., manufacturer vs. independent author, on- vs. off-label information, evidence of safety and effectiveness vs. HCEI). The guidelines enumerated by FDA in the Reprints Guidance would provide necessary safeguards with respect to publication of HCEI data in these journals, in that the Reprints Guidance protects the quality of distributed information, requires a disclaimer for any manufacturer involvement, and distinguishes between materials that are promotional and non-promotional in nature. Manufacturer dissemination of peer-reviewed HCEI that both satisfies the “competent and reliable” standard and tracks the Reprints Guidance is consistent with FDAMA Section 114’s goal to allow “the flow of [health care economic information] to experts who need it for patient and health plan decisions;” the HCEI published in these peer-reviewed journals, moreover, will undoubtedly be of higher quality and of greater value to payors than the company-generated data typically disseminated by manufacturers under the current regulatory scheme. We therefore request FDA to affirm that manufacturers may publish and share HCEI published in certain peer-reviewed journals and to expand the Reprints Guidance to explicitly cover such practices.

Id. The reference to adequate and well-controlled studies is not surprising in the context of off-label uses and given the level of substantiation typically required for safety and effectiveness claims.

16 The Journal of Managed Care Pharmacy is the journal of the AMCP, and Value in Health is affiliated with the International Society for Pharmacoeconomics and Outcomes ("ISPOR").


18 Indeed, FDA’s action in this regard would help address the asymmetry of the current regulatory scheme, which restricts the First Amendment rights of manufacturers to disseminate information about their products but permits other parties (e.g., researchers, clinicians, economists, professional societies) to share the same information. See id.

III. FDA Should Expressly Permit Manufacturers to Present HCEI at Managed Care and Other Payor Conferences

FDAMA Section 114 explicitly permits manufacturers to provide HCEI directly related to an approved indication and based on competent and reliable scientific evidence to a formulary committee or similar entity “in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations.” The law neither prohibits nor expressly permits manufacturers to present such information at managed care and other payor conferences, which the professionals who comprise such committees attend to learn about and share best practices for designing coverage programs that deliver high quality, cost-effective care.

FDA has offered no guidance to indicate whether, or to what extent, manufacturers may present on-label HCEI information at payor conferences. It has, however, provided a few considerations for the communication of off-label information in similar circumstances. As noted in the Citizen Petition, the safe harbor for “scientific exchange” allows companies to share truthful and nonmisleading data about their products—even if related to an unapproved use—at scientific meetings and conferences so long as the information is non-promotional and draws no conclusions regarding the safety and efficacy of the off-label use. The concept of scientific exchange, grounded in First Amendment concerns with broad restrictions of communication, and commensurate with the public interest in the dissemination of truthful medical information, furthers Congress’s aims in enacting FDAMA Section 114. In both cases, the goal is to encourage the flow of information to health care decision makers while retaining the necessary safeguards to ensure that the information shared is not deceptive or otherwise misleading. Accordingly, we request that FDA explicitly affirm that presentation of HCEI, related to approved indications and supported by competent and reliable scientific evidence, to payor audiences in attendance at managed care and other payor conferences, is a form of scientific exchange exempt from FDA’s advertising and labeling regulations provided that such presentations contain prominent disclosures of manufacturer support for or involvement in the development of the presented information.

IV. FDA Should Expressly Permit Manufacturers to Disseminate Health Outcomes Research to Payors

Finally, EMD Serono urges that FDA expressly permit manufacturers to disseminate health outcomes research that directly relates to an approved product indication and that is

20 See Citizen Petition, at 7-8. FDA has not adequately defined the parameters of this safe harbor but has acknowledged its existence numerous times.

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based on competent and reliable scientific evidence to those payor entities to which it may provide HCEI. While current law permits this information to be shared only if supported by substantial evidence, we believe that application of the competent and reliable standard to communications with payors is both appropriate and consistent with the purpose of FDAMA Section 114.

As Congress recognized in enacting that provision, formulary committees and similar entities charged with the selection of drugs have the requisite expertise to consider HCEI. Indeed, Section 114 defines “health care economic information” to include “any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention.” Congress recognized that this data is at the centerpiece of economic analyses, and payors commonly consider both clinical and economic outcomes in assessing the overall “economic value” of a particular product. Given the congressional determination that payors are qualified to interpret HCEI and its underlying bases, as well as payors’ demonstrated expertise in and desire for non-economic outcomes data, it is reasonable to conclude that the provision of health outcomes research to payors independent of any economic analysis is consistent with the statutory goal of FDAMA Section 114—not only would it facilitate high-quality, cost-effective care for health plan enrollees, but it would also limit promotional claims based on a different evidentiary standard to a uniquely qualified audience less susceptible to deception. Preventing manufacturers from sharing this information with payors would also constitute the type of content-based restriction on speech explicitly disapproved in Sorrell. Sorrell also suggests that restrictions on dissemination to sophisticated recipients is especially disfavored. Formulary committees are especially trained to evaluate this sort of data.

22 Although the information at issue is directly related to an approved product indication and is otherwise consistent with the conditions of use, outcomes research as a broad category has been characterized by FDA as constituting a “new use.” See Proposed Rule: Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 31,143 (June 8, 1998) (stating that “a different intended outcome (e.g., long-term survival benefit, improved quality of life, disease amelioration) from that stated in the label” represents a new use). The health outcomes research that EMD Serono would like to share with payors is truthful and non-misleading, and regardless of how it is characterized, would benefit the public health. See Citizen Petition at 3-5 (describing the value of truthful, non-misleading, off-label information and requesting clarity from FDA regarding permissible dissemination practices).

23 This is because claims based on health outcomes research convey information about treatment benefits of the product. See, e.g., 21 C.F.R. § 314.126.


25 The House Report for FDAMA Section 114 provides: “Incorporated into economic consequences are the costs of health outcomes. Data about health outcomes associated with the use of a drug, other treatments, or no treatment are therefore incorporated into the economic analysis.” See id.

26 See AMCP Format, at 2-16.

27 131 S. Ct. at 2663.

28 Id.
EMD Serono urges the agency to clarify through regulations or guidance that manufacturers may provide health outcomes information that relates to an FDA-approved indication and is based on competent and reliable scientific information to formulary committees and similar entities to aid these entities to establish formularies for managed care and other payors.

V. Conclusion

At a time in which federal health care policy is encouraging payors and providers to focus limited health care resources on providing quality, cost-effective care, FDA should adopt clear policies that enable manufacturers to share HCEI and health outcomes research about their products with those responsible for designing coverage and payment policies. As noted in the Citizen Petition, vagueness surrounding permissible manufacturer speech has significant consequences to manufacturers, the government, physicians, and patients. It also has significant consequences to payors governmental and private who rely upon manufacturers to provide information necessary to predict the specific benefits and costs that their products will have for their covered populations. Absent clarity regarding communications with formulary committees and other payor entities, many manufacturers will err on the side of caution and withhold communications. Ultimately, the under-communication of economically and clinically relevant information to payor entities has significant consequences for the public health. To ensure that payors have access to and manufacturers are able to provide this information, EMD Serono requests the agency to issue regulations or guidance embodying the policies outlined in these comments.

Sincerely,

Devin Smith
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