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Comparative Effectiveness Research: The Need for a Uniform Standard

By Scott Gottlieb, M.D., and Coleen Klasmeier

Reconciling a new comparative effectiveness research (CER) agency with scientific standards established in existing regulations would enable government agencies to share a consistent framework for making decisions based on CER. It would provide the kind of level playing field and clear guidelines that are needed to spur medical product developers and private payers to generate more of their own comparative evidence.

Legislative proposals to create a new federal agency focused on CER are moving ahead in the Senate, but thus far the legislative drafts have not set out the scientific corroboration that should be necessary before the research is used in support of policy decisions. Just as troubling is the failure of these proposals to consider existing federal regulations governing how the Food and Drug Administration (FDA) regulates the dissemination of precisely these kinds of research results. While the FDA's regulations speak to the quality of information that private companies can share with doctors and patients, the risk is that other agencies—principally Medicare—will use instead a much lower standard when they act on the federally advanced CER. This sets up an asymmetric playing field; policy and reimbursement decisions will be made in one agency based on data that a sister agency judges too unreliable even for purposes of private-sector sharing.

Engaging these issues now serves multiple goals. It establishes agreement around the level of rigor that ought to govern the conduct of CER. It also helps to avert inevitable conflicts between different government agencies over the

Scott Gottlieb, M.D. (scott.gottlieb@aei.org), is a resident fellow at AEI. Coleen Klasmeier (cklasmeier@sidley.com) is a partner and head of the FDA regulatory practice at Sidley Austin LLP.

Key points in this *Outlook*:

- Policymakers are interested in establishing a formal framework for comparative effectiveness research.
- A science-minded agency, such as the FDA, should establish guidelines about when information is sufficiently rigorous to be actionable by other government entities.
- The FDA's "substantial clinical experience" standard is appropriate for judging the veracity of CER. It is a standard that can be shared across the FDA and a CER agency. It passes legal muster, too.
- Budget estimates suggest CER will not reduce the deficit. We can expect then that CER will be used in the future to make decisions about access and pricing of medical products.
- We need to invest in the creation of a clinical trial infrastructure that enables more rigorous CER.

appropriate standards for making decisions based on the results of these studies. It is especially important that we grapple with how federal programs like Medicare will use the CER data. It is unrealistic to think we can prohibit Medicare from considering these studies. But we can develop a standard for weighing this evidence that recognizes that Medicare is no ordinary payer, since it drives decisions made by the entire health care market, and that the new CER agency will not be an ordinary research origination either. It will carry the government's imprimatur, elevating the impact of its work, and it will be under immediate political pressure to show economic and political payoffs for the investments that are being made in these research studies.

Ideally, the federal regulatory and policy criteria for sharing and acting on CER that are applied to private actors should reflect the same standards and principles applied to public agencies. The FDA, the federal agency responsible for the safety, efficacy, and proper labeling of prescription drugs and medical devices, has developed objective criteria against which statements based on CER could readily be adjudicated. Even though the kinds of study designs contemplated by the new CER agency fall short of the rigor that the FDA requires to support medical product approvals, the FDA's regulatory scheme includes alternative substantiation standards, one of which—"substantial clinical experience"—was specifically designed to assist in the analysis of data from CER-type studies. The FDA's current regulations can thus provide uniform criteria for determining when CER is sufficiently rigorous to form the basis of policy and regulatory decisions across different government agencies.

If we do not develop a common standard for substantiating CER, the FDA could be put into conflict with the new agency, and the private sector will be held to a much higher standard than the government when it comes to the degree of reliability that evidence must have to support decisions based on its findings. Government would control the field for developing CER, communicating the results and making reimbursement decisions based on the findings. Sponsors, who are subject to a higher standard enforced by the FDA, might not only be prohibited from sharing similar CER, but also be unable to comment on the results of the studies generated by the federal agency. The risk is that the government alone may become the sole arbiter of CER, since it alone would be exempt from FDA regulation. This could hurt consumers, who ultimately benefit from a competitive market for clinical information.

Reconciling Conflicts

These conflicts could be addressed by reconciling the evidence standards that the FDA applies to medical product companies with the standards used by other agencies (including Medicare) to assess and act on information from studies undertaken by the CER agency. With the adoption of a uniform understanding of the level of clinical substantiation needed to make government decisions based on the results of CER research, conflicts between federal agencies could be avoided, physicians and patients could have a clear understanding of the level of scientific substantiation that guides government decisions, and companies would have greater incentives to sponsor their own research, all thanks to a clear path and level playing field for sharing and acting on this kind of information.

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There are other benefits to involving the FDA in establishing these standards. The FDA can provide a rigorous check on the new CER agency. The fear of CER critics is that even in cases in which the information from the new agency might be inconclusive, it could nonetheless be used in a political way to support government decisions about access and pricing.[1] A science-minded agency like the FDA can provide a dispassionate actor in the process of establishing a framework for when CER information is sufficiently rigorous to be actionable by Medicare and other government entities. Medicare—and even the new CER agency—might be politically motivated to over- or underinterpret the resulting CER to support narrow policy goals.

These policy efforts also must recognize that establishing an evidence standard is not the same thing as assigning a "grade" to different CER studies based on

their relative utility. The principle for substantiation should primarily consider the threshold level of underlying rigor and the reliability of the finding to establish a benchmark for when a study should be deemed sufficiently thorough to be an actionable piece of information for regulatory and policy decisions. Many "grading" systems seek to encompass a wider variety of considerations about the practicality and political utility of the data in addition to their precision.[2]

In short, the FDA could become an important influence in creating a more robust and rigorous exchange of comparative clinical information about medical products. FDA regulations already establish that "substantial clinical experience"—which is a standard that applies to the kinds of population-based, epidemiological data used to develop much of the comparative research envisioned by the new CER agency—is an appropriate standard for companies to rely on when they seek to develop and share CER. The FDA's definition of "substantial clinical experience" can therefore, in turn, provide an ideal and consistent criterion to guide the level of substantiation needed for government agencies like Medicare to act on the results of studies issued by the new CER agency. To these ends:

- The FDA should develop a guidance document affirming that "substantial clinical experience" is an appropriate standard against which the FDA can evaluate comparative clinical studies that do not have the same design features as "adequate and well-controlled clinical trials" (which is the standard on which the FDA relies in making approval decisions). Although "substantial clinical experience" is a standard that currently exists in the FDA's regulations governing prescription drug advertising, there is no FDA guidance explaining how the standard might be used in the CER context.

- The FDA should develop guidance on the specific issues that arise when the "substantial clinical experience" standard is applied not only to CER-based statements made by medical product companies, but also to such statements made by the proposed CER agency. Adopting a common definition would help form a clear, consistent, and clinically defensible standard for both public- and private-sector sharing of CER and for guiding regulatory and policy decisions based on the results of this research.

- The FDA should develop a guidance document interpreting the "competent and reliable scientific evidence" standard for health care economic information.[3] The guidance document should establish a safe harbor enabling medical product companies to share a broad range of comparative information with sophisticated health care purchasers, such as health plans and Medicare. Ideally, the guidance would apply the "competent and reliable scientific evidence" standard not only to statements made in materials defined as "labeling" by the FDA, as the statute provides, but also to materials defined as "advertising" under the Food, Drug, and Cosmetic Act (FDCA).

- The public also needs to invest in the infrastructure for undertaking rigorous, prospective comparative studies that randomize treatment groups. We cannot rely solely on epidemiological data, and we cannot afford to commission prospective studies unless we have a more efficient process for undertaking them and more predictable standards governing when medical product companies in communications with payers, physicians, and patients can use data from those studies.

The Current FDA Paradigm for Comparative Research

The FDA standards governing medical product companies' distribution of comparative research results are often ambiguous. They are made still murkier by the inconsistent guidance that the FDA sometimes gives sponsors in private communications, coupled with the agency's reluctance to commit to any particular position in written guidance that could enable wider manufacturer communications of CER-type evidence held to a more applicable standard, rather than the agency's preferred substantiation standard—"substantial evidence."

Under current FDA regulations, companies can promote their products with claims of superiority over competing products—or over previous versions of a company's own products—but the FDA scrutinizes these claims with particular care. The agency holds superiority (and other comparative) claims to the "substantial evidence" standard, which is the same standard of substantiation that applies to the determination of whether a new product is entitled to marketing authorization.

The increasing demand for different types of comparative information that cannot satisfy the "substantial evidence" standard has made it harder for the FDA to continue insisting on a single standard. But the relative ease of applying one rule to all manufacturer claims makes it likely that the FDA would resist proposals to issue guidance encouraging manufacturers to distribute different kinds of information (like CER) based on any alternative standard.

The FDA generally believes that superiority claims are often misleading to consumers and clinicians and that the claims themselves are seldom complete. The FDA has not issued regulations or guidance documents specifically defining what constitutes a false or misleading claim in the CER context. In the absence of this kind of general guidance, insights about the agency's point of view come from reviewing FDA warning letters.[4] Over the years, the FDA has issued warning and "untitled" letters to medical product manufacturers alleging that comparative claims are false, misleading, or otherwise violative. The FDA has long required "substantial evidence" to support specific superiority claims. Its evidence requirement of two adequate, well-controlled, head-to-head trials is, in many cases, difficult to enroll and very expensive—amounting to an effective ban on superiority claims.

In May 2007, for example, the FDA issued an untitled letter concerning a doctor brochure for GlaxoSmithKline's Flonase (fluticasone propionate) nasal spray. Flonase is approved for seasonal allergic and perennial allergic rhinitis in certain patients. According to the letter, the brochure "misbranded" the drug because it made "unsubstantiated superiority claims that misleadingly imply" that Flonase was superior to a competing drug, Nasonex. The FDA found the presentations in the Flonase brochure misleading because the data did not constitute "substantial evidence" for two reasons.

First, the design of the study that compared Flonase to Nasonex did not contemplate a head-to-head comparison. So, the FDA said it is hard to rely on the data that were ultimately generated because the "study protocol" did not anticipate randomizing subjects to the two drugs. The FDA also said that the study was not replicated by a second study. Superiority claims, the FDA said, should be based on comparisons of the two drug products in "two adequate, well-designed, head-to-head clinical trials." Almost needless to say, the FDA letter reflects a more exacting standard for making comparisons than what will be offered by the research that is envisioned in legislative proposals for a new CER agency.[5] Few, if any, of the studies developed by a new CER agency would meet this existing FDA standard.

"Substantial Clinical Experience" as a Common Standard

Indeed, proponents of CER acknowledge that it will be rare to have multiple prospective, randomized clinical trials comparing two products. We will rely instead on epidemiological data, reviews of databases, and registries (in which patients are not randomly assigned to the different treatment groups). This kind of practical evidence forms the core of what the new CER agency intends to pursue. To accommodate this, we need a different standard of substantiation more appropriately matched to this kind of evidence.

Adopting a uniform definition for substantiation that is consistent across the FDA and the proposed CER agency would allow the FDA to play its traditional role in defining standards for making recommendations on the basis of research.

The FDA's "substantial clinical experience" standard encompasses a broader range of clinical data than the "substantial evidence" standard. "Substantial clinical experience" includes epidemiological data and registry data and is therefore an appropriate standard for judging the veracity of CER. Moreover, it is a standard that can be shared across the FDA and a CER agency, providing a uniform principle for weighing evidence.

Although some individuals inside the FDA's Division of Drug Marketing, Advertising, and Communications and elsewhere in the agency have been reported to tell some sponsors privately that the FDA does not strictly respect "substantial clinical experience" as an appropriate standard for substantiating comparative claims (creating ambiguity and uncertainty), the regulations governing prescription drug advertisements do set forth this standard. More important than whether there may be arguments supporting the view that "substantial clinical experience" does not apply to most drugs for which CER would be conducted is the fact that the FDA has gone so far as to promulgate a regulation defining "substantial

clinical experience." There are other evidentiary standards in the FDA's regulatory scheme, but none both fits the type of evidence likely to be generated by the proposed CER agency and already has a regulatory definition.

Public health is best served when the FDA issues definitive guidance that provides clear definitions and boundaries.[6] In this case, with so much policy interest in establishing a formal framework for CER, the FDA could play an important public health role by more clearly establishing how a definition of "substantial clinical experience" could assist in substantiating comparative research and deciding when sponsors should share this information with consumers and doctors and when government agencies should use this information for clinical and policy decision-making. Adopting a uniform definition for substantiation that is consistent across the FDA and the proposed CER agency would also allow the FDA to play its traditional role in defining standards for making recommendations on the basis of research.

Under current regulations, "substantial clinical experience" consists of experience "adequately documented in medical literature or by other data on the basis of which it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective" for the claimed uses.[7] The standard originally addressed the level of support a manufacturer had to provide for a claim about a drug that had not been evaluated by the FDA through the new drug application (NDA) process, which focuses on efficacy data from adequate and well-controlled clinical trials. But the language of the regulations is broad enough to apply to the substantiation of claims about any drug, including those that have been approved by the FDA.

There is credible legal support for an approach to CER that would rely on this interpretation of "substantial clinical experience." The very cornerstone of the FDA's legal authority to review the efficacy of new drugs recognizes the importance of information derived from "clinical experience." Section 505 of the FDCA not only makes clear that data developed outside of adequate and well-controlled clinical trials is vitally important to the FDA's assessment of the safety of a new drug, but also emphasizes the role of such data in the FDA's continuing assessment of safety after approval.

Indeed, section 505 contains the phrase "clinical experience" in a number of places. For example, section 505(k)(1) requires the holder of an NDA to "establish and maintain such records, and make such reports . . . of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug" that would enable the FDA to determine whether to invoke the withdrawal of approval provision in section 505(e).[8]

Pursuant to section 505(k)(1), the FDA has also issued a regulation requiring manufacturers to include in the NDA annual reports that they file with the agency "reports of clinical experience pertinent to safety (for example, epidemiological studies or analyses of experience in a monitored series of patients)."[9] According to this provision, reports of clinical experience include epidemiological analyses and analyses derived from observation of patients. This is precisely the kind of clinical information that forms the basis of studies that will be developed by a new federal CER agency.

The only way that CER would contain costs would be if Congress were to limit access to some high-cost treatments on the basis of the data.

The FDA's "substantial evidence" regulations explain what "substantial clinical experience" does *not* mean. The signal characteristic of "substantial evidence," according to the FDA, is that it is generated from "adequate and well-controlled clinical trials."[10] A reasonable interpretation of "substantial clinical experience" is that it is not necessarily derived from such trials.

Although few companies, if any, have energetically embraced the "substantial clinical experience" standard due to the lack of a clear pathway set forth by the FDA in publicly available guidance, the regulations clearly contemplate the use of this alternative substantiation standard in the context of promotional claims. The FDA should make clear in guidance that any manufacturer is permitted to provide comparative effectiveness information directly to physicians and even to patients if the information satisfied the standard and was truthful and nonmisleading. This is consistent not only with the FDCA itself, but also with other FDA regulations that expressly provide for manufacturers to furnish price, in addition to benefit and risk, information directly to consumers in promotional communications.

In short, there are enough provisions in the existing FDA regulatory framework to guide the development of a clear, thorough, and consistent definition of "substantial

clinical experience" that could be used as a standard for substantiating claims based on CER data across both the FDA and a new CER agency. This would create a uniform standard and level playing field for the sharing of this kind of information.

The Argument for a Uniform Standard

It is unrealistic to believe that, over the long run, this federally generated CER will not be used by other federal agencies such as Medicare to inform decisions about access to and pricing of medical products. Notwithstanding efforts by political proponents of a CER agency to assuage critics by punting on this fundamental question, logic reveals the eventual outcome.

Budget estimates also betray the true intentions of CER proponents. Office of Management and Budget director Peter R. Orszag has cited the Obama administration's support of CER as one of the principal ways to control health care spending.[11] Yet, on three separate occasions, the Congressional Budget Office (CBO) has said that there would not be any savings derived from the new federal CER effort. The first found that one CER proposal (H.R. 3162) would increase federal spending by $1.1 billion over ten years.[12] The second also found that government funding for CER only increases the federal deficit for the first ten years.[13] Then–CBO director Orszag issued a third estimate in testimony before Congress on June 12, 2007, when he stated that CER might not yield direct savings for at least ten years.[14] The only way that CER would contain costs would be if Congress were to limit access to some high-cost treatments on the basis of the data. This is an unfashionable truth policymakers will not publicly acknowledge. As a result, under CBO rules, policymakers cannot claim savings in official budget estimates, even if cost containment—and rationing—remains their goal. The administration's claims about savings, however, reveal the underlying intentions.

It is unlikely that we will receive more political candor about these goals. But it is reasonable to expect proponents to define the clinical and legal standards on which information could be shared and policy recommendations made based on the results of CER. It is hard to envision that the new CER agency will not be issuing press releases, policy papers, and other material that interprets and trumpets the results of its research. What will be the scientific basis for how the new agency interprets its findings and issues its recommendations?

Absent some agreement about the standards for substantiating CER, the proximate result is likely to be a plethora of debatable and uninterruptible research developed by a network of health systems researchers with a vested financial and intellectual interest in the promotion of this research. There will be political pressure to overinterpret the findings in order to justify the expenditure. There is also risk that the FDA evidentiary standards will become less relevant. The end result would be confusing drug information that does not correspond to clinical practice, let alone the way government health plans make reimbursement decisions.

Moreover, if payers were to begin to make reimbursement decisions based on data standards less rigorous than the FDA's requirements, it would diminish incentives for sponsors to seek supplemental approvals for already-marketed products. The additional claims would not have economic value if government payers were willing to base reimbursement decisions on less rigorous and easier-to-execute research studies.

One of the benefits of existing regimes, such as the statistical standard that p must equal 0.05 in order for the result from a randomized clinical trial to be deemed "significant," is that these standards provide a framework for making objective medical decisions. It provides a clear line for actionable results. It may not be an optimal standard for certain kinds of medical decision-making, and some argue that the widespread application of p=0.05 provides an unnecessarily binary basis for making decisions. But it does reveal the benefits of having some objective criteria to substantiate how decisions are made based on new information.

When it comes to CER, no similar standards exist. Truth will be in the eye of the researcher—or the agency with the most incentive and clout to shape the interpretation of a result. That exposes the fundamental risk in this scheme. Without agreement around the objective standards for substantiating CER, there will be an overinterpretation of the results by politically conflicted government agencies. It is true that standards to govern the substantiation of less rigorous epidemiological data—the kind of information generated by a new CER agency—will never have sharp boundaries like p=0.05. Nor is it desirable to create a grading system, since inherent in such a process is subjective interpretation that masks uncertainties. Instead, the standards embedded in FDA regulations provide consistent and applicable criteria for weighing this kind of clinical evidence. "Substantial clinical experience" provides a reasonable standard for

decision-making across the FDA, Medicare, and the new CER agency.

Based on the text of the FDCA and of FDA regulations, "substantial clinical experience" can be interpreted to mean experience in a monitored series of relatively heterogeneous patients who are administered a drug for treatment purposes outside the clinical trial context.[15] To qualify as "substantial," the monitoring must be conducted in a manner that helps assure the data generated from the patients are sufficiently reliable. By operation of the definition of "substantial clinical experience," the information from the observed patients must be "adequately documented," and it must be appropriate for "qualified experts" to conclude from the information that the drug has the attributes it is claimed to have.[16]

To adopt this definition as the standard used to substantiate CER across federal agencies, the FDA should first and foremost issue guidance that specifically addresses comparative efficacy claims about approved products based on data from CER-type studies. This guidance should explain clearly how manufacturers could use "substantial clinical experience" as an appropriate standard of substantiation for CER claims in promotional material.[17] Once this standard is memorialized in guidance, the new CER agency can bridge easily to this definition as a basis for recommending when its resulting research reaches an adequate level of rigor and substantiation for purposes of being relied upon by other parties.

The FDCA also contains the "competent and reliable scientific evidence" standard, in section 502(a), which was amended by the Food and Drug Administration Modernization Act (FDAMA) in 1997 to state specifically that a manufacturer can provide "health care economic information" to selected managed-care organizations without risking that the materials the manufacturer uses to convey this information would be regarded by the agency as false or misleading. This standard is limited by the lack of FDA interpretive guidance and by the language of the provision itself, which refers to health care economic information provided to certain managed-care organizations and does not, therefore, currently provide a safe harbor for manufacturer statements about the comparative cost-effectiveness of medical products directed to health care practitioners or patients.[18] In guidance, the FDA could affirm that "competent and reliable scientific evidence," which is a standard used in a provision of the FDCA expressly allowing manufacturers to provide written materials containing CER information to managed-care organizations and public payers, includes the kinds of study designs likely to be supported by a new CER agency, specifically epidemiological databases and nonrandomized series.[19]

If the FDA were to provide guidance, the "competent and reliable scientific evidence" standard could provide a more limited but still important pathway for manufacturers to provide CER-type information to sophisticated managed-care entities and health care purchasers. Such guidance would establish a safe harbor for sponsor-generated CER as being appropriate for sharing with health plans, including Medicare.[20] Although a pathway for sharing this information is defined in the FDCA as amended by FDAMA, ambiguity remains around the permissibility of this sort of information exchange, and some sponsors are reluctant to share CER with payers.

While there is a place in medical research for studies based on registries and epidemiological data, we cannot rely on these less rigorous and less precise clinical trial constructs alone, especially to answer difficult clinical questions.

The FDA had started addressing pharmacoeconomic claims' substantiation issues before Congress enacted the "competent and reliable" standard in 1997, but there has been since then no meaningful guidance from the FDA regarding the meaning of that standard. One of the factors creating a disincentive for sponsors to develop information about the cost-effectiveness of various treatments is that their ability to share this information remains needlessly murky, owing to FDA reluctance to delineate clear guidelines.[21]

Finally, the kinds of clinical trial constructs being contemplated by a new CER agency (epidemiological databases, registries, nonrandomized simple large trials) are unreliable, especially when it comes to examining differential responses to treatments within smaller populations of patients. For many drug regimens, for example, the operative question is not whether one drug is best for everyone, but who should take which drug and under what circumstances. There are real clinical differences not only between similar patients, but also when

a drug gets started and stopped. Epidemiological studies of databases will not detect the clinical signals that provide answers to these questions. More rigorous trials are needed, often prospective trials that randomize similar patients to different treatment groups.

The question is how to develop more of this kind of research without spending tens of millions of dollars. The reason that less rigorous clinical trial constructs have become the sine qua non of a new CER agency is that they can be achieved with modest funding. Undertaking more rigorous clinical studies (which are also more definitive) can cost dollars on the pennies spent on currently proposed CER study designs. A single large, prospective, randomized trial can cost $100 million or more. While there is a place in medical research for studies based on registries and epidemiological data, we cannot rely on these less rigorous and less precise clinical trial constructs alone, especially to answer difficult clinical questions.

The cancer cooperative groups maintained by the National Cancer Institute (NCI) have developed a model and a good track record for how we can build a clinical trial infrastructure in other therapeutic areas to enable more rigorous comparative research to be undertaken more efficiently. U.S. investments in CER should also include the creation of a clinical trial infrastructure that enables this kind of more rigorous research. We need to invest in our capacity to conduct rigorous CER. Most of the studies that the NCI sponsors through its network are, at their core, comparative trials, since they are mostly comparing current regimens to regimens in which a new agent is added to standard care. NCI has also had success at engaging more community physicians and academic researchers in the clinical trial process. This is another important goal for a new network created for undertaking rigorous CER, since many of the clinical questions that we want to answer involve decisions made in the community rather than at academic hospitals.

There are models for how rigorous clinical research can be conducted more efficiently using web-based data entry and centralized institutional review boards. These and other approaches can reduce the paperwork and compliance costs of enrolling subjects in clinical trials. Ultimately, the best way to translate the findings from the research process is to enlist community physicians in the conduct of the studies. There is no reason a new CER agency needs to rely solely or largely on less rigorous data constructs like databases and registries.

Conclusion

We should continue to press proponents of a CER agency on the sustainability of their own assumptions. They insist that the resulting CER data will save the health care system hundreds of millions of dollars, but they deny that Medicare reimbursement decisions will eventually be tied to the results. Most reasonable people will understand that these two objectives are incongruous. Most reasonable people know that CER will eventually be used to tweak coverage decisions.

But as the political effort to frame this prospective new agency's mandate takes shape, we also need to engage CER proponents directly in a serious discussion about the standards that should be used for making policy decisions based on the results of the research they espouse. To these ends, "substantial clinical experience" provides a good starting point for decisions about the substantiation needed for sponsors to share information from their own CER—and about the criteria government health programs like Medicare should be held to when the resulting information is ultimately used as support for their reimbursement policy decisions.

Notes

1. Scott Gottlieb, "Congress Wants to Restrict Drug Access," *Wall Street Journal*, January 20, 2009, available at www.aei.org/article/29219.

2. The government should have to follow a binary system of substantiation, rather than a graduated one, but it should recognize that companies, unlike the government, have First Amendment rights to make claims based on any level of substantiation, as long as they are truthful and nonmisleading.

3. See *Food, Drug, and Cosmetic Act*, section 502(a), as amended by the *Food and Drug Administration Modernization Act of 1997*.

4. Jeffrey K. Shapiro, "Comparative Claims: Legally Permissible, but Proceed with Care," *Medical Device & Diagnostic Industry* (September 2004), available at www.devicelink.com/mddi/archive/04/09/014.html (accessed June 4, 2009). Technically, statements in warnings and untitled letters do no more than to allege a legal violation; they do not necessarily reflect any official Food and Drug Administration (FDA) policy and do not bind the FDA to the views expressed in the letters. (*Code of Federal Regulations* 21, § 10.85[k].)

5. Congressional Budget Office (CBO), *Budget Options*, vol. 1: *Health Care* (Washington, DC: CBO, December 2008), available at www.cbo.gov/doc.cfm?index=9925 (accessed June 4, 2009).

6. FDA, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, "Promotional Material Review Process."

7. *Code of Federal Regulations* 21, § 202.1(e)(4)(ii)(c).

8. *U.S. Code* 21, § 355(k)(1).

9. *Code of Federal Regulations* 21, § 314.81(b)(2)(vi).

10. *Code of Federal Regulations* 21, § 202.1(e)(4)(ii)(b).

11. Gregory Twachtman, "Comparative Effectiveness in U.S. Will Not Be NICE, OMB's Orszag Says," The Pink Sheet Daily, March 5, 2009.

12. CBO, "Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role" (CBO paper 2975, Washington, DC, December 2007), available at www.cbo.gov/doc.cfm?index=8891 (accessed May 17, 2009).

13. Gregory Twachtman, "CBO Holds Line on Comparative Effectiveness' Lack of Initial Savings," The Pink Sheet Daily, January 5, 2009.

14. Gregory Twachtman, "Savings from Expanded Comparative Effectiveness Could Be Decade Away—CBO," The Pink Sheet, June 18, 2007.

15. *Code of Federal Regulations* 21, § 202.1(e)(6)(ii).

16. *Code of Federal Regulations* 21, § 202.1(e)(4)(ii)(c).

17. FDA warning and untitled letters do not contain any commentary on the regulatory definition of "substantial clinical experience," and the FDA has not provided relevant guidance.

18. Other existing FDA regulations and policies—such as its policy on responses to unsolicited requests, the regulations allowing promotion based on price (but not cost-effectiveness), and the scientific exchange provision of the investigational new drug regulations—are similarly limited.

19. *Food and Drug Administration Modernization Act of 1997*, section 114, codified at *U.S. Code* 21, § 352(a).

20. A similar approach, using enforcement discretion to create a safe harbor for distribution of certain information, is the basis for at least one recent guidance document. See 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 Drugs and Approved or Cleared Medical Devices," January 2009, available at www.fda.gov/oc/op/goodreprint.html (accessed June 4, 2009).

21. Kate A. Stewart and Peter J. Neumann, "FDA Actions against Misleading or Unsubstantiated Economic and Quality-of-Life Promotional Claims: An Analysis of Warning Letters and Notices of Violation," *Value in Health* 5, no. 5 (2002): 390–97; P. J. Neumann, K. Claxton, and M. C. Weinstein, "The FDA's Regulation of Health Economic Information," *Health Affairs* 19, no. 5 (2000): 129–37; and Monica Schultz and Chris Lyle, "Health Economic Analysis: What Needs to Be Considered When Designing a Clinical Trial for Medical Technology," *Applied Clinical Trials* (May 2009), available at http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/Trial+Design+Articles/Health-Economic-Analysis/ArticleStandard/Article/detail/597463 (accessed June 4, 2009).