Washington Legal Foundation
Advocate for freedom and justice®
2009 Massachusetts Avenue, NW
Washington, DC 20036
202.588.0302

Critical Legal Issues: *WORKING PAPER SERIES*

COMPARATIVE EFFECTIVENESS: Refining the Standards for FDA Approval & CMS Coverage

By
Areta L. Kupchyk
Kathleen H. McGuan
Reed Smith LLP

Washington Legal Foundation
Critical Legal Issues WORKING PAPER Series

Number 165
May 2009

TABLE OF CONTENTS

ABOUT WLF'S LEGAL STUDIES DIVISION

The Washington Legal Foundation (WLF) established its Legal Studies Division to address cutting-edge legal issues by producing and distributing substantive, credible publications targeted at educating policy makers, the media, and other key legal policy outlets.

Washington is full of policy centers of one stripe or another. But WLF's Legal Studies Division has deliberately adopted a unique approach that sets it apart from other organizations.

First, the Division deals almost exclusively with legal policy questions as they relate to the principles of free enterprise, legal and judicial restraint, and America's economic and national security.

Second, its publications focus on a highly select legal policy-making audience. Legal Studies aggressively markets its publications to federal and state judges and their clerks; members of the United States Congress and their legal staffs; government attorneys; business leaders and corporate general counsel; law school professors and students; influential legal journalists; and major print and media commentators.

Third, Legal Studies possesses the flexibility and credibility to involve talented individuals from all walks of life - from law students and professors to sitting federal judges and senior partners in established law firms - in its work.

The key to WLF's Legal Studies publications is the timely production of a variety of readable and challenging commentaries with a distinctly common-sense viewpoint rarely reflected in academic law reviews or specialized legal trade journals. The publication formats include the provocative COUNSEL'S ADVISORY, topical LEGAL OPINION LETTERS, concise LEGAL BACKGROUNDERS on emerging issues, in-depth WORKING PAPERS, useful and practical CONTEMPORARY LEGAL NOTES, interactive CONVERSATIONS WITH, law review-length MONOGRAPHS, and occasional books.

WLF's LEGAL OPINION LETTERS and LEGAL BACKGROUNDERS appear on the LEXIS®/NEXIS® online information service under the filename "WLF" or by visiting the Washington Legal Foundation's website at www.wlf.org. All WLF publications are also available to Members of Congress and their staffs through the Library of Congress' SCORPIO system.

To receive information about previous WLF publications, contact Glenn Lammi, Chief Counsel, Legal Studies Division, Washington Legal Foundation, 2009 Massachusetts Avenue, NW, Washington, D.C. 20036, (202) 588-0302. Material concerning WLF's other legal activities may be obtained by contacting Daniel J. Popeo, Chairman.

ABOUT THE AUTHORS

Areta L. Kupchyk served as FDA Associate Chief Counsel for Drugs and Biologics between 1993 and 2003. She is a partner at Reed Smith LLP and focuses on FDA regulatory counsel within the Life Sciences Health Industry Group.

Kathleen H. McGuan served as Chief Counsel for CMS and Associate General Counsel of HHS between 2005 and 2007. She is Senior Counsel and Strategic Advisor to the Life Sciences Health Industry Group at Reed Smith LLP.

Jamie L. Schreiber and **Catherine A. Hurley**, Reed Smith associates, also contributed to this WORKING PAPER.

COMPARATIVE EFFECTIVENESS: Refining the Standards for FDA Approval & CMS Coverage

By
Areta L. Kupchyk
Kathleen H. McGuan
Reed Smith LLP

INTRODUCTION

Money talks. The recent $1.1 billion federal allocation for comparative effectiveness research under the American Recovery and Reinvestment Act of 2009 tells us that the government is more serious than ever about gathering data on the relative effectiveness of medical treatments. How the data will be used by the government and third party payors is the question that may be worth billions of dollars more. A fear that patients, doctors, and innovators may lose more than they gain is fueling the political, legal, and scientific debate that will determine how we compare products and use data from such comparisons. Everyone has an interest in this debate.

The people most interested in comparative effectiveness (CE) can be divided into three general groups: government; patients and physicians; and medical product innovators and makers. It is no secret that the government wants to reform the health care system and lower its Medicare and Medicaid costs. That patients and doctors want to know more about the relative safety and effectiveness of treatment options is second only to knowing that the

treatments are safe and effective.[1] That drug and device makers need incentives to keep investing billions of dollars into research and development is the American reality for medical innovation. Balancing these interests fairly, ethically, and with competent scientific evidence is in everyone's interest . . . and nothing less will do.

The CE debate unavoidably implicates two federal agencies: the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS). FDA is responsible for determining whether drugs and devices have been shown, by convincing scientific evidence, to be *safe and effective for their intended uses*.[2] CMS is responsible for making coverage decisions for new medical technologies based on whether the items and services are "*reasonable and necessary* for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[3] Neither agency is expressly authorized to determine or consider the comparative effectiveness of drugs or devices in carrying out its statutory mandate. Of the two agencies, however, FDA has actually begun to interject a comparative effectiveness element into its review of certain drugs. FDA's rationale appears to be based on the agency's interpretation not of the term "effectiveness" but of "safety."

---

[1]According to a recent poll by National Public Radio, the Kaiser Family Foundation, and the Harvard School of Public Health, a majority of U.S. residents believe that electronic health records would improve the coordination and quality of medical care (Joseph Shapiro, NPR.org, Apr. 22, 2009).

[2]*See* 21 U.S.C. §§ 355 and 360c(a)(2).

[3]42 U.S.C. § 1395y(a)(1)(A) (emphasis added).

I. THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (FDCA) AND FDA REGULATIONS

The terms "safe" and "safety" when used as a standard for approval of a drug or device are not defined in the FDCA nor in FDA regulations.[4] The FDCA states that FDA may not approve a drug unless (among other things) there are "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling . . . ."[5] Although FDA has not promulgated a regulation or issued formal guidance providing its interpretation of this statutory provision, FDA uses a risk/benefit analysis as is evident through the agency's informal communications. For example, FDA frequently warns that "there is no such thing as [a] completely safe [medicine]. All medicines have risks. FDA approval of a drug simply means that the benefits outweigh the known risks."[6] When FDA approves a drug as safe, the approval is always subject to the conditions of use set forth in the product's approved labeling.

---

[4]Although not defined within the context of FDA's approval standard, the term "safety" is defined in general to mean: "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." 21 C.F.R. § 600.3(p).

[5]21 U.S.C. § 355(d).

[6]*See, e.g.*, FDA Website, "Be an Active Member of Your Health Care Team," http://www.fda.gov/usemedicinesafely/active_member_article.htm (last visited Apr. 27, 2009). *See also* FDA Website, "Managing the Risks From Medical Product Use: Report to the FDA Commissioner From the Task Force on Risk Management" (May 1999), http://www.fda.gov/oc/tfrm/executivesummary.html (last visited Apr. 27, 2009); *FDA Consumer Magazine*, "Cancer Drugs: Weighing the Risks and Benefits" (Jan.-Feb. 2007), http://www.fda.gov/fdac/features/2007/107_cancer.html (last visited Apr. 27, 2009).

The FDCA definition of "effectiveness" is equally formulaic. To be considered effective under the FDCA, there must be "substantial evidence" that the drug will be as effective as it is claimed to be under the conditions of use in its proposed labeling. The FDCA defines "substantial evidence" to mean convincing evidence from "adequate and well-controlled clinical studies."[7] The FDCA does not require that a new drug be better than, *or even as good as*, any approved product or existing therapy.

FDA was given the authority to require drug makers to submit evidence of effectiveness in 1962 when Congress amended the FDCA by passing the Drug Amendments of 1962.[8] That the effectiveness standard is not, and was never intended to be, a comparative standard is distinctly noted in the legislative history of the Drug Amendments of 1962. When the legislation was pending, the Secretary of the Department of Health, Education, and Welfare (now the Department of Health and Human Services), Abraham Ribicoff, reassured a nervous Congress that "the bill furnishes no basis for . . . apprehensions" and that FDA would make approval decisions based on "comparative efficacy of a new drug in terms of drugs already on the market." The Secretary further stated that "[w]e do not seek the authority . . . . [and] we would not and do not intend and do not want to pass on relative efficacy. This is no power we seek and no

[7]21 U.S.C. § 355(d). Generally, FDA requires two adequate and well-controlled clinical trials, although in some cases FDA is authorized under the FDCA to accept one such trial as substantial evidence.

[8]The Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

power we desire."[9] The FDA Commissioner at that time similarly assured Congress that, in rendering drug approvals, FDA would not consider the "relative efficacy" of one drug compared with another.[10]

Clearly, Congress did not intend to give FDA authority to use a comparative efficacy standard to approve drug and device products. Had Congress so intended, it would have expressly granted such authority. For example, FDA has explicit authority to require bioequivalence data to show that a generic drug product is the same as an innovator drug product.[11] FDA has also used notice and comment rulemaking to implement a superiority requirement for an orphan drug that would otherwise be barred by the marketing exclusivity of another orphan drug product for the same indication.[12] Indeed, notice and comment rulemaking, as required under section 4 of the Administrative Procedure Act (APA), may only be bypassed if the agency action amounts only to an interpretive rule, general statement of policy, or rule of agency organization, procedure, or practice.[13] When an agency imposes an approval requirement that has a "substantial impact on the regulated industry, or an important class

[9] *Hearings before the Senate Subcomm. on Antitrust and Monopoly of the Comm. on the Judiciary*, 87th Cong. 2585, 2605 (1961).

[10] *Id.* at 2606.

[11] 21 U.S.C. § 355(j).

[12] *See* 57 Fed. Reg. 62,085 (Dec. 29, 1992); 21 U.S.C. § 360aa; 21 C.F.R. § 316.25(a)(3).

[13] 5 U.S.C. § 553(b)(A). *See Chrysler Corp. v. Brown*, 441 U.S. 281, 301 (1979) (distinguishing between substantive rules and interpretive rules).

of the members or the products of that industry, notice and opportunity for comment should first be provided."[14]

Nevertheless, in 1962, FDA began asking drug and device makers to submit relative efficacy data to obtain marketing approval, and the industry complained. These complaints were noted in a 1995 White House report, sometimes referred to as the Clinton-Gore Reinvention Report. This report proposed a long list of FDA regulatory reforms to "reduce or eliminate" regulatory processes without lowering health and safety standards, including one "reform" to address industry's complaints that FDA had been imposing comparative effectiveness requirements thus creating "unreasonable difficulties in developing new therapies and bringing them to market."[15] The Clinton-Gore Reinvention Report stated when it would be "essential for public health protection that a new therapy be *as effective* as alternatives that are already approved for marketing . . . " (emphasis added.) For example, comparative effectiveness data would be required when:

> 1. the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack); or
>
> 2. the disease to be treated is a contagious illness that poses serious consequences to the health of others (e.g., sexually transmitted disease).[16]

---

[14]*Pharmaceutical Manufacturers Ass'n v. Finch*, 307 F. Supp. 858, 863 (D.Del. 1970).

[15]President Bill Clinton and Vice President Al Gore, "Reinventing Regulation of Drugs and Medical Devices," National Performance Review (Apr. 1995), http://govinfo.library.unt.edu/npr/library/reinvent(drug&medical%20devicereg).htm (last visited Apr. 27, 2009).

[16]*Id.*

The Clinton-Gore Reinvention Report also described when evidence of less effectiveness would be acceptable.

> . . . [N]ew products are often developed for particular subpopulations who either do not respond to or are not able to tolerate an existing approved therapy. FDA will generally approve for use in such a subpopulation a product that is shown to have effectiveness in this group, regardless of whether the product can be shown to be as effective in the broad target population as the alternative therapy. This is because, in effect, there is no available alternative therapy for the subpopulation. For example, a number of patients cannot tolerate a widely used therapy for an AIDS-related pneumonia. FDA approved the drug atovaquone for use in these patients, even though it had been shown to be less effective than the standard therapy when tested in a broad population.[17]

FDA's policy on drug comparisons was reaffirmed in September 2008 when Dr. Robert Temple stated that FDA will ask for comparative information "where lesser effectiveness would represent a safety concern. . . . . [For example,] marked inferiority . . . of anti-psychotics and antidepressants to standard treatment is 'not safe.'" However, Dr. Temple acknowledged that non-inferiority and comparative studies are difficult to interpret because the differences between drugs is smaller than between drug and placebo; thus, in many cases, a much larger study would be needed.[18]

---

[17] *Id.*

[18] *See* Robert J. Temple, MD, PowerPoint presentation entitled "Comparative Effectiveness: FDA Activities," http://www.nhpf.org/library/handouts/Temple.slides_09-26-08.pdf (Sept. 26, 2008) (last visited Apr. 27, 2009). Dr. Temple is Associate Director for Regulatory Policy in FDA's Center for Drug Evaluation and Research. Dr. Temple also noted that "marked inferiority" is not yet well-defined.

Despite such acknowledgements, FDA appeared to have applied a comparative efficacy requirement in at least one case. In July 2008, FDA issued a "not approvable letter" to Vanda Pharmaceuticals, Inc. even though Vanda *had* demonstrated the effectiveness of iloperidone, an investigational atypical antipsychotic. FDA told Vanda that it had shown iloperidone to be superior to placebo in patients with schizophrenia and similar to the active comparator, ziprasidone; but FDA expressed concern about the comparative efficacy of iloperidone to risperidone, which Vanda had used in prior studies. FDA told Vanda to do an additional trial comparing iloperidone to placebo and to olanzapine or risperidone to demonstrate the compound's efficacy further.[19] In a surprise decision, however, FDA approved iloperidone on May 6, 2009 after Vanda submitted a complete response to the not-approvable letter without additional comparative effectiveness data. Although FDA appears to have pulled back from requiring comparative effectiveness data for approval, the specter of a CE requirement remains.

II. THE SOCIAL SECURITY ACT (SSA): MEDICARE NATIONAL COVERAGE DECISIONS

In 1965, the SSA authorized Medicare to cover a wide range of medical services, including medical devices, surgical procedures and diagnostic services, so long as the items and services are "reasonable and necessary" for diagnosis or

[19] *See* Vanda Press Release at http://phx.corporate-ir.net/phoenix.zhtml?c=196233&p=irol-newsArticle&ID=1179851&highlight (last visited Apr. 28, 2009).

treatment.[20] The SSA did not define this "reasonable and necessary" standard and CMS has not promulgated a rule establishing criteria for applying the standard. Generally, the standard has been "understood to reflect the prevailing views of the physician community."[21]

In 1989, however, CMS did try to establish specific criteria for its "reasonable and necessary" determinations. CMS, then the Health Care Financing Administration (HCFA), proposed to cover a new technology if it was accepted by the medical community as safe, effective, not investigational, appropriate, and cost-effective.[22] Among other criticisms, the use of cost-effectiveness was opposed and the negative comments led HCFA not to adopt the proposed rule.[23] Although there are still no formal criteria for making coverage decisions, CMS is subject to modest limitations, including a prohibition against interference with the practice of medicine.[24] In addition, the statute restricts the agency's ability to use prescription drug claims data, which

[20]42 U.S.C. § 1395y(a)(1)(A).

[21]Peter J. Neumann et al., *Medicare's National Coverage Decisions, 1999-2003: Quality of Evidence And Review Times*, HEALTH AFFAIRS, 24, no. 1 (2005), 243-254.

[22]HCFA, "Medicare Program Criteria and Procedures for Making Medical Services Coverage Decisions That Relate to Healthcare Technology," Proposed Rule, 54 Fed. Reg. 4,302 (Jan. 30, 1989).

[23]HCFA, "Medicare Program; Procedures for Making National Coverage Decisions," General Notice, 64 Fed. Reg. 22,619 (Apr. 27, 1999).

[24]*See* 42 U.S.C. § 1395.

is collected in order to pay claims under Medicare Part D, for any other purpose.[25]

However, in 2008, using its general authority under the SSA, CMS finalized a rule permitting the use of claims data being collected for Part D payment purposes for other research, analysis, reporting, and public health functions.[26] CMS explained that these data were needed "to oversee Medicare, protect the public's health, and respond to Congressional mandates." Although the vast majority of comments on the final rule agreed, noting the benefit of using the data for, among other things, determining the "efficacy of prescription drugs," some raised concerns about the "inherent limitations associated with the use of claims data" for "research."[27] According to the preamble, CMS intends to pool claims data from various Medicare benefits to evaluate comparative effectiveness, using hospitalizations as an outcome measure. CMS specifically stated that "[a]ccess to [Medicare] Parts A, B, and D claims data will allow the Secretary to analyze the prescription drug utilization of chronically ill patients over time, and determine whether increases in prescription drug utilization do, in fact, result in fewer hospitalizations."[28] However, to the extent that claims data will be used for comparative effectiveness research (especially any research

[25]*See* 42 U.S.C. §§ 1395w-115(d)(2)(B) and (f)(2).

[26]CMS, "Medicare Program; Medicare Part D Claims Data," Final Rule, 73 Fed. Reg. 30,664 (May 28, 2008).

[27]*Id*. at 30,665.

[28]*Id.* at 30,666.

that could govern Medicare coverage), CMS acknowledged that the reliability of the data, which is inherently incomplete, is an important concern:

> We believe the implementation of disease management programs and the evaluation of these programs could potentially be strengthened by the use of Part D claims data. However, we believe these data must be used with caution for these purposes since we collect Part D claims data only for Medicare Part D enrollees. We do not collect drug claims data for those beneficiaries who receive their drug insurance solely from other sources . . . .[29]

III. COMPARATIVE EFFECTIVENESS RESEARCH TODAY

Under the American Recovery and Reinvestment Act, the National Institutes of Health (NIH) and HHS will each receive $400 million, and the Agency for Healthcare Research and Quality (AHRQ) will receive $300 million for comparative effectiveness research. An HHS Coordinating Council for Comparative Effectiveness Research (the Council) will coordinate the use of the funding and make recommendations on how to spend the money. The Council will also issue an annual report to Congress with recommendations. NIH has already designated its allocation for dissemination to researchers through its Challenge Grant program. NIH has proposed dozens of comparative effectiveness research studies, including research on cancer treatments, fibromyalgia, use of biologics in autoimmune rheumatic and skin diseases, mental health interventions, and chronic childhood arthritis, musculoskeletal

[29] *Id.* at 30,671.

and skin disease.[30] A primary component of each of these proposed research studies is cost effectiveness as well as comparative effectiveness.

How the data from comparative research will be used is not specified and has thus generated concerns from drug and device makers and patients and their doctors. These groups, and their federal congressional representatives, have raised concerns that comparative effectiveness would be used as a basis for denying access to appropriate but expensive treatments; discounting the individual needs of individual patients; stifling or ignoring advances toward personalized medicine; overlooking gender, race, and ethnic differences because research studies often do not include enough women or people of color; ignoring differences based on broad population averages; rationing healthcare; intruding in the patient-physician relationship; and superseding medical judgment in the practice of medicine. Of equal concern are the possibilities that comparative effectiveness data would provide impetus for centralized government healthcare control, price controls, under-funding of institutional care, arbitrary restrictions on access to new therapies, and a significant decrease in venture capital to support medical innovation.

These fears become greater when considering the inherent limitations of clinical research methodologies, *i.e.*, study designs, used to generate comparative effectiveness data. Dr. Temple highlighted these limitations in his

[30] *See* NIH Challenge Grants in Health and Science Research (RC1), Comparative Effectiveness Research (CER), http://grants.nih.gov/grants/funding/challenge_award/ (last visited Apr. 27, 2009).

2008 presentation. He noted that cross-study comparisons are "almost never credible"; epidemiological data is "not credible when looking at tiny differences (10-20%)"; in most settings, study results are "*only*" persuasive and informative "if superiority [is] shown; and "real 'equivalence' is very hard to show [unless there are] very large studies."[31]

IV. THE STANDARDS FOR FDA APPROVALS AND CMS COVERAGE DECISIONS

Such statements by FDA's Associate Director of Regulatory Policy suggest the types of study designs that FDA would require (or refuse to accept) when asking for comparative effectiveness data. The legal question, however, is whether FDA has the authority to condition approval of medical products on comparative data. The plain language of the FDCA does not provide such authorization. Basic rules of statutory construction require one to consider the fact that there is an absence of explicit authorization under the drug and device approval provisions, while there is explicit authority only in discrete circumstances, to require comparative effectiveness data.[32] Clearly, Congress was capable of adding comparative effectiveness criteria to FDA's drug and device approval considerations. Indeed, in light of Congress's own concerns and

[31]*See* infra, note 18.

[32]*See Wyeth v. Levine*, 129 S. Ct. 1187 (Mar. 4, 2009) (noting that when Congress enacted an express pre-emption provision for medical devices, it declined to enact such a provision for prescription drugs). Similarly, had Congress wanted FDA to use comparative effectiveness in drug approval determinations, it would have expressly provided FDA with the authority to do so, as it did with respect to bioequivalence data for generics.

its intentional omission of such authority in 1962, the need for explicit statutory authority is difficult to deny.

Imposing a comparative effectiveness requirement to obtain marketing approval has a substantial impact on a discernable and significant class of regulated industry. Specifically, any manufacturer of a drug or device that is intended to treat a disease that is "life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack); or * * * [a] contagious illness that poses serious consequences to the health of others (e.g., sexually transmitted disease), would be subject to the requirements."[33] As it did (and was required to do) when establishing the orphan drug superiority requirement to sidestep the exclusivity of another orphan drug, FDA is required to follow notice and comment rulemaking before expanding the standard for drug approval.[34]

The desire by CMS to consider comparative effectiveness data and cost effectiveness data in making its coverage decisions is obvious. The Administration's healthcare reform agenda and the systemic economic problems of the day heighten this prospect. Like FDA, however, CMS has no explicit authority to consider the comparative effectiveness or cost effectiveness of medical treatments when making coverage decisions. Interjecting such

[33] *See* infra, notes 15 and 18.

[34] *Pharmaceutical Manufacturers Ass'n v. Finch,* 307 F. Supp 858, 863 (D.Del. 1970). *See Baker-Norton Pharmaceuticals, Inc. v. FDA and Bristol-Myers Squibb*, 132 F. Supp. 2d 30 (D.D.C. 2001); *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996).

criteria, particularly after CMS withdrew a proposed rule to do just that, would at the very least require notice and comment rulemaking.

CONCLUSION

Given the difficulties in developing competent and useful comparisons of effectiveness and the limitations on FDA and CMS to use such data, we should expect a long road and have a right to comment before any uses of such research data are employed.