

FDA Regulation Of Off-Label Promotion: An Answer

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The FDA-approved labeling for prescription drugs contains only the information that FDA has found essential to uses for which the manufacturer has provided “substantial evidence” of efficacy in accordance with strict regulatory standards. As a result, the labeling, while authoritative, is incomplete. Changes in the environment for prescribing decisions, including the increasing importance of comparative effective research (CER) information, make it timely to consider reforms to the current regulatory framework for drug labeling. This paper sets forth a proposal for legislative adjustments to the Federal Food, Drug, and Cosmetic Act to make the approved labeling for drugs more pertinent to clinical decisions by providing for the inclusion of a more heterogeneous mix of information from CER sources and clinical trials not meeting the traditional “substantial evidence” standard—without abandoning a central role for FDA review. These reforms would not only clarify the rules governing manufacturer distribution of off-label use information but also enhance patient care by improving prescribing decisions.

Off-label uses of drugs play a critical role in health care. By definition, off-label uses lack an official Food and Drug Administration (FDA) finding of effectiveness, because they have not successfully completed the approval process that is the mechanism for getting them into labeling. The FDA nonetheless has established policies that allow drug manufacturers to provide physicians with information about off-label uses. The purpose is to aid in clinical decision making, which often involves drug uses not spelled out *in haec verba* in approved labeling. The FDA’s “safe harbors” include criteria that limit manufacturers’ information-providing activities: if a communication respects those limitations, then the FDA ordinarily will not intend to use the communication as evidence of intended use in an enforcement action against the manufacturer. The FDA approach is one of “delicate balance”—of forbidding off-label promotion without undue incursion into the ability of physicians to obtain information about off-label uses from manufacturers.

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The safe harbors are hard to navigate. They all use broad and vague terms, and often use multi-factorial tests rather than bright-line standards. One of them, involving the long-standing FDA policy allowing manufacturers to provide information about off-label uses in response to “unsolicited requests,” for many years existed only in a one-page memorandum from 1982. Today, it is set forth in a single paragraph in a 1994 Federal Register notice. Until FDA published a guidance document in 2009 in which that notice was cited, it was not entirely clear whether the policy, while technically binding on the agency, as a practical matter had force and effect.¹ The other “safe harbor” policies are similarly buried, their contours and status hard to discern.

In response to a request from several manufacturers, the FDA has announced its intention to revisit the safe harbors, starting with the unsolicited requests policy and the regulatory safe harbor for “scientific exchange” about off-label uses. The questions on which the FDA notice is asking for comments indicate that, at least at this early stage, agency officials are thinking of changing the scientific exchange safe harbor so that whether communication qualifies as permitted scientific exchange depends on factors such as the identity of the speaker. The FDA took a similar approach in a guidance document on off-label speech in the context of continuing medical education supported by manufacturer funding, and that guidance document has proven very hard to apply in practice. Recent court decisions emphasize that this lack of clarity has an important constitutional dimension.

This paper sets forth a proposal to reform the regulatory framework governing off-label promotion. The cornerstone of the proposal is a change to the Federal Food, Drug, and Cosmetic Act—the principal source of the FDA’s legal authority and the basis for the government’s “off-label promotion” prosecutions—under which a new use of an approved drug could be incorporated into

¹ In December 2011, FDA published a proposal to describe the unsolicited requests policy in a new guidance document, though it remains to be seen whether the draft will ever be finalized and in what form.

the labeling of the drug even if it did not satisfy the “gold standard” of evidentiary support applicable to initial approvals.

I. The Problem of Off-Label Promotion

The Federal Food, Drug, and Cosmetic Act of 1938 (as amended) does not say anything about “off-label promotion” in those terms. Instead, it says three things of relevance. First, a manufacturer cannot say anything false or misleading in its labeling. Second, a manufacturer must provide, with its drug, labeling that contains “adequate directions for use.” Third, a manufacturer can only market a “new drug” after getting FDA’s permission, and that permission comes after the manufacturer submits an application containing data and information from different sources—most importantly, trials of the drug in human beings.²

THE LAW OF OFF-LABEL PROMOTION

FDCA § 502(a), 21 U.S.C. § 352(a): A drug shall be deemed to be misbranded if its labeling is false or misleading in any particular

FDCA § 502(f)(1), 21 U.S.C. § 352(f)(1): A drug shall be deemed to be misbranded unless its labeling contains adequate directions for use

FDCA § 505(a), 21 U.S.C. § 355(a): No new drug may be introduced or delivered for introduction into interstate commerce without a new drug application (NDA) or abbreviated NDA

The off-label promotion problem reflects the accretion of administrative interpretations over the years. According to those interpretations, the whole scheme boils down to one principle: a manufacturer must not intend for its product to be put to any unapproved use.

Whether a particular use not spelled out in the approved labeling is an off-label use is hard to know. “A new use,” the agency said in 1998, “is one that would require approval or clearance of a

² 21 U.S.C. §§ 352(a), 352(f)(1), 355(a), (b), (d); 21 C.F.R. § 314.50.

supplemental application in order for it to be included in the product labeling.”³ In the FDA’s opinion, an unapproved use can mean a completely different indication; modification of an existing indication to include a new dose, a new dosing schedule, a new route of administration, a different duration of usage, a new age group (e.g., unique safety or effectiveness in the elderly), another patient subgroup not explicitly identified in the current labeling, a different stage of the disease, a different intended outcome (e.g., long-term survival benefit, improved quality of life, disease amelioration), effectiveness for a sign or symptom of the disease not in the current labeling; and comparative claims to other agents for treatment of the same condition.⁴ The test that the FDA applies is so inextricably linked to the exercise of judgment that no manufacturer can determine with certainty, *a priori*, whether a particular deviation from the labeling would qualify as off-label.

Whether a use is “intended” is similarly hard to discern. Under the more expansive interpretations of the FDCA, if a drug manufacturer “intends” that its product be used off-label, then the manufacturer has committed a legal violation. A manufacturer cannot know whether it has the requisite unlawful “intent” in advance to any degree of certainty because of the shifting positions the government has taken on the issue. The Department of Justice, on the FDA’s behalf, has investigated many companies for FDCA violations, focusing primarily or even exclusively on internal company documents reflecting a desire or expectation on the part of company officials to “book” sales of their products for off-label uses. More recently, the government and a senior FDA official submitting a statement in support of the government’s brief in a particular case asserted that either or both of promotional claims recommending an off-label use and the “circumstances” surrounding distribution of the drug could provide evidence of illegal “intent.” The inconsistency of the government’s statements, in litigation and elsewhere, have bedeviled industry attempts to divine clear rules to govern their conduct. Moreover, these cases do not typically go to court, so there are no judicial

³ 63 Fed. Reg. 31,143, 31,145 (June 8, 1998).

⁴ *Id.* at 31,143.

interpretations to provide the missing but all-important clarity, and the precise contours of the government theories remain largely uncharacterized.

The analysis is further complicated by the existence of regulations expressly allowing promotion of a drug under conditions unaddressed in the labeling in certain circumstances. Many scenarios appear to involve off-label promotion but in actual fact involve the permitted non-promotional distribution of off-label information. The FDA recognizes that the public health is actually served by a certain amount of manufacturer distribution of information about off-label uses. As a result, there have developed over several decades a number of statements of policy from the agency explicitly allowing manufacturer activities that include off-label use information. The tangle of rules and policies actually reflects important public health considerations.

Manufacturers could simply decline to share any information about any new uses until after FDA approval, but that approach would create serious problems. First, if a manufacturer could not provide any information about new uses, then it would be impossible to conduct clinical trials of those uses because the manufacturer would be unable to provide the “investigator’s brochure” that FDA regulations require. The point of the brochure is to give the investigator—the physician actually conducting the trial on the manufacturer’s behalf—sufficient information to be able to fulfill his or her responsibilities under the protocol for the trial. For the trial to proceed, the physician must be told the purpose of the investigation, which necessarily means the manufacturer must provide information about the potential effectiveness of the product. To some, this communication could resemble promotion.

Second, in many cases the manufacturer is legally required to provide information about new uses of its approved drug products to the public. Disclosure requirements can arise out of federal securities laws or from legislation requiring manufacturers to disclose information about their clinical trials on

www.clinicaltrials.gov. These latter provisions actually require manufacturers to post their clinical trial results on-line for public review. The possibility of off-label promotion liability for doing just that has led FDA officials to make public assurances that manufacturers releasing their off-label efficacy results will not ordinarily be punished for violating the FDCA. The implication is that otherwise the manufacturers' disclosures could constitute a violation.

Third, FDA actually encourages manufacturers to disseminate information about new uses to encourage physicians to use approved products optimally in patient care. In other words, a strict regime would hurt the public health, in the FDA's view, because a certain level of "off-label promotion" is helpful in guiding clinical decisions. The various types of "promotion" that the FDA encourages through its policies have been identified over many years. At least four types of what is arguably "off-label promotion" are expressly allowed by the most well-known FDA "safe harbors."

One safe harbor, in FDA regulations, provides that the rule forbidding the "commercialization" of an investigational new drug is not to be construed to interfere with a manufacturer's entitlement to engage in "scientific exchange." The FDA also has a long-standing policy of allowing manufacturers to provide information about "new uses" of approved products "in response to unsolicited requests." The FDA has issued a guidance document enabling manufacturers to distribute peer-reviewed medical literature about new uses of approved products. Manufacturers can also provide financial support for third-party providers of continuing education for health care professionals, even if that education discusses off-label uses. These four "safe harbors" are all important regulatory mechanisms encouraging manufacturers to provide information about the promising new uses of their products to prescribers and even to patients. To safeguard against abuses, each policy also includes limitations and recommendations, such as the condition on responses to unsolicited requests that the information provided must be non-promotional and "balanced."

Additional FDA policies allowing the distribution of off-label use information have not been embodied in any publicly available document. Under one of these, manufacturers are permitted to promote their products off-label to non-U.S. physicians at medical meetings as long as they make sure that the promotion is carefully limited and does not include U.S. physicians. The basis for the practice is not a statutory or regulatory provision or even a non-binding “guidance” document issued by the FDA. Rather, manufacturers are effectively allowed to engage in off-label promotion in that limited situation in reliance on a 2002 memorandum written by a medical professional society. The memorandum recorded a conversation between the society’s representatives and FDA officials. Although it never “saw the light of day,” manufacturers have safely relied on it for nearly ten years, and the FDA has not taken any enforcement action contrary to it.

Manufacturers settle off-label promotion cases for a number of reasons. Of course, many of the settled cases involve government allegations that, if true, would reflect undeniably unlawful conduct. But the absence of full-blown litigation means the facts are never tested before a neutral arbiter. Moreover, although it is impossible to know the full range of reasons even in any single case, it seems obvious that a major precipitating factor for the settlements of the past twenty years is the elusiveness and complexity of the regulatory regime itself. The “rules” the manufacturers are expected to follow often are not written down anywhere (or at least, nowhere that anyone can find easily), or are impossible to apply in any specific situation. The “safe harbors” use terms that are vague or are interpreted differently by FDA over time, and in any case are recognized by prosecutors only in the breach.⁵

⁵ Brief of the National Spasmodic Torticollis Association, the National Spasmodic Dysphonia Association, Allied Educational Foundation, and Washington Legal Foundation as Amici Curiae in Support of Plaintiff’s Motion for Preliminary Injunction, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. dismissed 2010).

II. Barriers to the Incorporation of Emerging Efficacy Information Into Drug Labeling

Manufacturers have difficulty managing regulatory risks in this arena not only because the speech-regulatory rules are complex and hard to decipher, but also because of regulatory impediments to the approval of new uses for inclusion in the approved labeling. It is expensive and time-consuming to get new uses approved by the FDA. The agency has high expectations of the data and information that need to be submitted to support a supplemental approval. Typically, the FDA expects the same kind and amount of clinical data and information to substantiate the efficacy of a new use as it requires for an initial approval—the “substantial evidence” standard of Section 505. It is sometimes hard to enroll the required number of subjects in clinical trials to support a supplemental approval with the approved drug already available in the marketplace. Physicians do not want to recommend that their patients agree to be subjects in trials if it means they would have to risk being randomized to an arm of the trial that receives placebo or some less effective active control.

In some cases, to generate the kind of data needed for regulatory purposes, the manufacturer would have to conduct the kind of study that would involve the assignment of some study participants to a control, when the experimental drug has already become the “standard of care” therapy. Although this occurs relatively infrequently, it is not unheard of, and in such cases it is virtually impossible to accrue the number of subjects necessary for the results to be valid according to principles of statistical analysis generally imposed by the FDA.⁶

Even where the impediments to a full-blown “registration” trial are not as pronounced, manufacturers and others using the drug may have generated data suggesting, but not proving to the FDA’s satisfaction, that the drug is safe and effective in circumstances not set forth in approved labeling. Physicians are entitled to, and often do, conduct “investigator-initiated trials” of approved

⁶ 21 C.F.R. § 314.126(b)(7).

drugs to explore potentially effective new uses. They also accumulate anecdotal evidence of a drug's efficacy—information that is extraordinarily important to the ongoing assessment of drug as it is used in a more diverse patient population than in clinical trials before approval. As a result, after approval, a steady stream of information about a drug becomes available, and this information often is highly relevant to patient and prescriber decisions about the use of the product.

Under the current framework, that information may, or may not, ultimately become incorporated into the official labeling for the drug. This information cannot be added if it fails to meet the statutory standard of “substantial evidence.”

III. Prior Reform Efforts

Over the years various entities have advanced proposals for measures to address the off-label promotion problem. Previous legislative proposals have sought to require the FDA to develop a Federal Drug Compendium containing “relevant information,” above and beyond that included in FDA-approved physician labeling, about drugs to promote their “proper use”⁷; or by adding new safe harbors to the FDCA for certain off-label use information sources deemed sufficiently accurate to alleviate the concerns ordinarily presented by manufacturer involvement.⁸ The closest antecedent to the proposal outlined in this paper was an undeveloped suggestion to provide for the addition of information about off-label uses to a separate section of the approved labeling if accompanied by supporting references to studies in peer-reviewed medical literature.⁹ All of these proposals received some limited consideration in Congress but did not make meaningful progress.

⁷ S. 2755, § 155 (1978), reprinted at 124 Cong. Rec. 7203, 7222 (March 16, 1978).

⁸ H.R. 1742, § 7 (1995); H.R. 3199, § 20 (1996).

⁹ *See* FDA Unlikely to Self Reform; Congress Must Act, Observers Say, Health Care Policy Rep. (BNA), at D-28/Mar. 20, 1995.

The FDA has also sought to address the problem. In 1997, FDA launched a “New Use Initiative,” the expressed purpose of which was “to speed up the development of new and supplemental uses of medications by using all available data to determine the effectiveness of drugs and biological products.” According to the FDA’s March 13, 1997, press release announcing the program, the aim was to provide the industry with clear guidelines regarding the agency’s ability to find a drug effective for a new use despite the absence of data satisfying the traditional “substantial evidence” standard.

The public explanation for the initiative relied on scientific advances that enabled the FDA to simplify the approval process and to find efficacy using “extrapolat[ion] from existing efficacy data” or other methods—without watering down the “gold standard” on which the FDA had built its reputation since 1962. The FDA did not emphasize the off-label issue in the release, but the final sentence referred to the agency’s desire to

“improve the supplemental application process for sponsors of all approved products with promising but unlabeled uses.”

“New Use Initiative” (1997)

New uses approved based on data other than those “collected during new multiple trials”:

- Beta-interferon (Betaseron) (a biological product) labeled for ameliorating symptoms in multiple sclerosis based on two effectiveness findings from one multicenter study
- Enalapril (for heart failure) labeled for treating symptoms and improving survival based on two different effectiveness findings, each from a different study
- Ibuprofen (non-steroidal anti-inflammatory drug) and ondansetron (a treatment for chemotherapy-induced nausea) labeled for pediatric use based on extrapolation from adult data because “the course of the disease and the beneficial effects of the drug are sufficiently similar for both adults and children”

The initiative produced two new guidance documents—one outlining the FDA’s general policy of finding new uses effective using alternative approaches in appropriate cases and another, oncology-specific document providing information about the evidence that the FDA would deem sufficient for supplemental applications for cancer treatments. The FDA’s initiative covered both drug and biological product approvals, even though the FDA historically had licensed biological products based on data from a single study in some cases. The initiative failed, because neither guidance document did anything to reduce the burden on manufacturers to submit data from conventional clinical trials to demonstrate the efficacy of a new use.

Although one of the guidance documents described the agency’s intention to find new uses effective based on alternative approaches, the FDA had been doing just that for many years. The problem was that these alternatives did not meaningfully relieve the burden on manufacturers, because the liberalization of the standards was not dramatic enough to allow into the labeling the kinds of data and information that the manufacturers were likely to have on hand. Moreover, manufacturers did not rush to submit supplemental applications because there was no mechanism to assure relatively prompt review, and no guarantee of approval.

Shortly after the FDA announced the “New Use Initiative,” Congress sought to address the off-label promotion problem by crafting a new provision of the FDCA intended to serve as a grand compromise between the two sides of the debate. It amended the FDCA by enacting the Food and Drug Administration Modernization Act (FDAMA), Section 401 of which expressly permitted companies to provide certain off-label information—reprints of peer-reviewed medical journal articles reporting on clinical investigations—on condition that they have pending with the FDA a supplemental application for the use. The FDA moved relatively quickly to promulgate implementing regulations, but the legislation fell quickly into disuse and expired by its own terms in 2006. The legislation also amended the statutory provisions governing the NDA review process to

make clear that a single study could suffice for approval, consistent with the FDA's statements in connection with the earlier-announced "New Use Initiative."

FDAMA did not provide an enduring solution to the off-label promotion problem, because it failed to recognize that limiting a manufacturer's ability to communicate about new uses to the distribution of journal articles and similar sources would not be adequate to provide patients and prescribers with relevant information to support clinical decisions. It also provided for the distribution of reprints and similar information only if the manufacturer was going to submit a supplemental application to FDA. In essence, it sought to use the carrot of the "safe harbor" established by Section 401 to get manufacturers to submit more supplemental applications. Because of the resources necessary to satisfy that condition, and its limited scope, the provision was never used in any meaningful way.

A few years later, during Commissioner Mark McClellan's tenure at the FDA, the agency convened an "Unlabeled Use Task Force." Information about the task force's mandate and activities is not public, and reportedly the group disbanded soon after its creation due to internal disagreement over fundamental questions of law and policy. But it was reported that the task force was intended to develop potential solutions to the off-label promotion problem. In 2009, the FDA issued new guidance in an effort to clarify when manufacturers could provide reprints and reference texts about new uses to physicians. The purpose of the guidance was to address a gap in the regulatory scheme that had been created by the sunset of Section 401 of FDAMA. For a variety of reasons, manufacturers often do not use this pathway for the distribution of scientific information about new uses.

IV. The Proposal

The proposal described in this paper involves changes to the current regulatory system, to make it easier for manufacturers to add efficacy information to the official, FDA-approved labeling. The

vehicle for the change would be an amendment to Section 505 of the FDCA, which sets forth the “substantial evidence” standard for drug efficacy. Section 505 defines “substantial evidence” generally to mean that a manufacturer must provide to the FDA data from two “adequate and well-controlled” clinical investigations in order to obtain approval for a new drug. This standard is the main obstacle to the addition of new uses to approved drug labeling, because—under current law—it also applies to supplemental indications of already-approved drugs.

Section 505 would be amended by adding a third evidentiary standard. In addition to the default “two studies” interpretation long favored by the FDA and the slightly less demanding “one study plus confirmatory evidence” standard added by FDAMA in 1997, Section 505 would have a special rule for efficacy supplements submitted for already-approved new drugs. The special rule would state that, if the preponderance of evidence related to a drug use shows that the drug is effective, or shows that the therapeutic benefits of the use generally outweigh its risks, then the labeling must state that there is evidence that the drug is effective for that use. This standard—“preponderance”—already appears in FDA prescription drug labeling regulations, but it currently only operates to require drug labeling to *disclaim* common off-label uses. Section 505 would also, under this proposal, be amended to provide for the inclusion in approved labeling of a new section that lists references supporting the efficacy of the off-label uses for which the “preponderance” standard has been satisfied.

Additional language in the amended statute would rely on other provisions of existing regulations to address the inclusion of information in approved labeling when a particular off-label use is common. To address the situation in which physicians lack dosing information about common off-label uses and the lack of such information creates a patient safety issues, the statute would provide that the holder of an approved application may commence distribution of a drug product accompanied by revised labeling upon receipt by the agency of a supplement for a change to the application to reflect

newly acquired information to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product. The statute could also be rendered consistent with an FDA regulation providing that a specific warning relating to a use not provided for under the Indications and Usage section of labeling may be added if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard. These provisions would codify existing regulations that the FDA has adopted but that are not often invoked.

Statutory change is necessary because of institutional impediments to a more discretionary regulatory standard. As the reliance on existing regulations discussed above reflects, the current regulatory scheme already provides for the inclusion of information in approved drug labeling beyond what has been substantiated according to the substantial evidence standard. Manufacturers are extremely reluctant to invoke these provisions, because the FDA officials responsible for premarket review make clear in their communications with manufacturers that they want labeling above all to avoid any even indirect suggestion of off-label uses. That means that manufacturers cannot, as a practical matter, revise drug labeling to warn against off-label uses, despite the provisions of the law to the contrary, without risking the displeasure of the government officials primarily responsible for signing off on drug approvals. Nor can they add to labeling information that would increase the safe off-label use of a drug, such as dosing information, without accepting the same risk. Not even a Supreme Court case holding that manufacturers are primarily responsible for maintaining the accuracy of drug labeling has meaningfully changed the industry's practice of making only those revisions to labeling expressly requested by the FDA review divisions within the drug center. Consequently, the only way to reform the regulatory system is through legislative changes that directly constrain the FDA's discretion.

As noted, the current system requires a drug manufacturer to limit its labeling statements about efficacy to those that the FDA has found are supported by “substantial evidence.” The source of this requirement is Section 505 of the FDCA, under which the FDA must refuse to approve a new drug if “there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.” The phrase “substantial evidence” is defined in the statute to mean “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

The FDA generally takes the position that “clinical investigations” in the statute, because it is plural, means that more than one study is required to demonstrate efficacy. In 1997 Congress amended the statute to make clear that in certain cases something less than data from one trial augmented by data from a second, confirmatory study would be sufficient. The 1997 amendment states that, “If [the FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness,” then the FDA “may consider such data and evidence to constitute substantial evidence” Although the FDA has found many drugs effective without insisting on data from two studies, it is hard to know *a priori* in any particular case whether two studies will be required, and the existence of the “substantial evidence” standard in the statute enables agency officials to reserve the right to find a drug ineffective for a use if the manufacturer does not provide data from two trials. In any case, the two-trial standard remains the prevailing one.

Because the statute establishes a high bar for the inclusion of efficacy information in the approved labeling for a new drug, the FDA regards the labeling as the authoritative regulatory statement of the conditions in which the use of the product is appropriate and reflects an acceptable risk-to-benefit ratio. FDA regulations governing the content of the labeling explicitly characterize that document as “a summary of the essential scientific information needed for the safe and effective use of the drug.”¹⁰ With respect to the uses for which a drug has been found effective, the FDA rules state that the labeling “must be based whenever possible on data derived from human experience,” and that “[n]o implied claims or suggestions of drug use may be made if there is . . . a lack of substantial evidence of effectiveness.”¹¹ The authoritative status of labeling, based on the key limitation that only efficacy information supported by “substantial evidence” would be included, led the FDA in 2006 to describe the labeling as “a compilation of information about the product, approved by FDA, based on the agency’s thorough analysis of the new drug application (NDA),” “contain[ing] information necessary for safe and effective use.”¹²

The principal deficiency with the idea that the approved labeling is the authoritative source of information about the safe and effective use of the drug is that it ignores the realities of clinical practice. Physicians do not regard labeling as central to clinical decision making or to patient care, and there is even evidence that physicians are simply unaware of the unapproved versus approved uses of prescription drugs. As early as 1972, the FDA acknowledged that physicians make treatment decisions based on information and judgments having nothing to do with the labeling, stating that “[t]he physician is . . . responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling *and other*

¹⁰ 21 C.F.R. § 201.56(a)(1).

¹¹ *Id.* § 201.56(a)(3).

¹² 71 Fed. Reg. 3,922, 3,922 (Jan. 24, 2006).

*adequate scientific data available to him.*¹³ The agency's adoption of a guidance document to facilitate the distribution of scientific and medical journal articles describing off-label uses reflects physician reliance on the literature in addition to (or rather than) the labeling in many clinical settings.

The FDA's concerted effort to control the content of labeling belies the reality that the labeling is rapidly becoming irrelevant to actual medical practice. In 2006 the agency recognized that the "increase in the length, detail, and complexity of prescription drug labeling" was "making it harder for health care practitioners to find specific information and to discern the most critical information."¹⁴ The FDA therefore developed a new format for the labeling, which put the most important information (identified through physician surveys conducted by the FDA) at the beginning of the document. The revised format made the information in the labeling easier to find, but it did not make the information itself more relevant, because the rule did not alter the basic principle that the efficacy information in labeling should be limited by the "substantial evidence" standard. Nor did legislative initiatives intended to speed the development and approval of drugs intended for serious or life-threatening diseases, or orphan conditions, alter the statutory "substantial evidence" standard.

Changing the standard applicable to the FDA's evaluation of the efficacy of new uses would enable manufacturers to incorporate information about those uses into approved labeling more easily, without necessarily having to have data from two adequate and well-controlled clinical trials. The change would reduce the regulatory disincentives currently affecting manufacturer decisions whether to revise labeling to include new-use information. It would also increase the clinical relevance of drug labeling by including more information about the actual uses of drugs and even comparative effectiveness information in labeling, as that, too, is effectively forbidden under the current regime.

¹³ 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972); *see also id.* (not only labeling but also "medical articles, tests, and expert opinion" may "constitute evidence of the proper practice of medicine").

¹⁴ 71 Fed. Reg. at 3,922.

Comparative effectiveness information could be eligible for inclusion in approved labeling according to a revised statutory standard as well. Because such information almost always comes from analyses that fall short of the existing “substantial evidence” standard, the statute would have to be amended to make clear that comparative effectiveness information is permitted in labeling if it is truthful and non-misleading and relates to a use for which the substantial evidence standard is met or to a use for which the more inclusive “preponderance” standard is met. The effect of such a statutory change would be to make the labeling relevant to clinical decisions in the further respect of providing a convenience source of information regarding the effectiveness of a drug relative to its costs.

The proposal is intended to be moderate and modest. It does not contemplate the end of the new drug approval scheme as we know it, though pending legislative proposals (e.g., advocating a “totality of the evidence” standard under Section 505) could have that effect. Rather, it *reinforces* the importance of FDA review by providing for manufacturer submission of supplemental applications for a broader range of emerging uses than before. At the same time, changing the evidentiary standard of efficacy for new uses is bound to be seen by some as a frontal assault on the FDA’s regulatory powers. It has taken agency officials decades to develop a regulatory infrastructure to implement the substantial evidence standard for most new products, and senior FDA leaders remain staunchly committed to the “gold standard” for reasons of public health and also to safeguard the FDA’s preeminence among drug regulatory agencies worldwide.¹⁵

The reality, however, is that the FDA’s implementation of the substantial evidence standard has not been doctrinaire. The FDA has an established policy of encouraging NDA submissions for new uses of approved cancer drugs by bending the statutory efficacy standard to near breaking. The agency has issued regulations expressing its commitment to “flexibility” in interpreting the substantial

¹⁵ Robert Temple, Food and Drug Administration, Center for Drug Evaluation and Research, Washington, DC, USA, A regulator’s view of CER, Clin Trials 2011 Oct 5; Margaret A. Hamburg, M.D., Shattuck Lecture. Innovation, Regulation, and the FDA, N Engl. J. Med.;363:2228-32 (2010).

evidence standard. The FDA also, in 1998, published a guidance document describing the circumstances in which it would find “substantial evidence” without requiring data from two studies. New drug approvals since 1997 show that the FDA has found substantial evidence of efficacy without two studies.¹⁶ All of those agency actions involved *initial* drug approvals whereas the proposal advanced in this paper only concerns subsequent indications.

The proposed change, to succeed in encouraging the submission of more supplemental applications for new uses, would almost certainly have to be accompanied by user fees. Currently, the FDA takes many months to review supplementary applications for approved drugs. That is because (1) there are user fee performance metrics for initial approvals that do not extend to efficacy supplements and (2) there is some sense that the public health need for swift review is less compelling because, once approved, a drug can lawfully be put to any use deemed clinically appropriate by the physician in the practice of medicine. If a physician can lawfully obtain the drug because it has already been FDA-approved, and the physician also has access to information—outside of the approved labeling—about how to use the drug off-label, then there is no compelling need for the FDA to devote scarce resources to the review of that new use. Indeed, the FDA has spent many months reviewing supplemental submissions for new indications, even in oncology, despite the agency’s expressed desire for manufacturers to submit efficacy data for new uses and have those data subjected to the scrutiny that the agency review process affords.

¹⁶ Coleen Klasmeier & Torrey Cope, NDA Approval Under FDCA Section 505(b)(1) Based on Effectiveness Data from One Clinical Trial (Soc. Sci. Res. Net., Working Paper, January 10, 2012), available at <http://ssrn.com/abstract=1991427>.

TIME TO APPROVAL OF SUPPLEMENTAL APPROVALS FOR ONCOLOGY DRUGS, JAN. 2009 – APR. 2011

DRUG	CANCER TYPE	DAYS TO APPROVAL
AFINITOR® (everolimus)	Progressive neuroendocrine tumors of pancreatic origin (PNET)	181
AVASTIN® (bevacizumab)	Glioblastoma	186
AVASTIN® (bevacizumab)	Metastatic renal cell carcinoma	304
DACOGEN® (decitabine)	Myelodysplastic syndrome	307
EMEND® (aprepitant and fosaprepitant dimeglumine)	Anti-emetic	395
FASLODEX® (fulvestrant)	Hormone receptor positive metastatic breast cancer	301
FUSILEV® (leucovorin calcium)	Advanced metastatic colorectal cancer	839
GLEEVEC® (imatinib)	Philadelphia + chronic myeloid leukemia	299
HERCEPTIN® (trastuzumab)	HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	183
RITUXAN® (rituximab)	Follicular, CD20-positive, B-cell non-Hodgkin's lymphoma	303
SPRYCEL® (dasatinib)	Chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia	291
SPRYCEL® (dasatinib)	Chronic myeloid leukemia	183
TARCEVA® (erlotinib)	Locally advanced or metastatic non-small cell lung cancer	394
TASIGNA® (nilotinib hydrochloride monohydrate)	Philadelphia chromosome positive chronic myeloid leukemia	188
TYKERB® (lapatinib ditosylate)	Hormone positive and HER2-positive advanced breast cancer	304
XGEVA® (denosumab)	Prevention of skeletal-related events in patients with bone metastases from solid tumors	183
ZEVALIN® (ibrutinomab tiuxetan)	Follicular non-Hodgkin's lymphoma	276

V. Conclusion

The Federal Food, Drug, and Cosmetic Act should be amended to make the approved labeling for drugs more pertinent to clinical decisions. Through targeted amendments, the FDCA should provide for the inclusion of a more heterogeneous mix of information, including comparative effectiveness information and other clinical data not meeting the traditional “substantial evidence” standard. Unlike other proposals, this one does not alter the FDA’s central role in the evaluation of efficacy data. Instead, it provides for more information from a wider range of sources to be incorporated into labeling on a more reasonable timetable. These reforms are likely to be seen by many FDA officials as highly intrusive, because it arguably alters in a fundamental way the main statutory authority governing the content of efficacy claims for approved new drugs. But it would, if implemented, both enhance patient care by improving prescribing decisions, and also clarify the rules governing manufacturer distribution of off-label use information.

Under the proposal outlined in this paper, more scientific information about new uses would be brought into the labeling, and manufacturers would be permitted to promote their products based on that information. The labeling would contain an enriched body of more clinically meaningful information, and their claims would not be limited to statements that the FDA has concluded satisfy the “substantial evidence” standard. The basic idea behind the proposal is straightforward: if the “off-label problem” is that manufacturers want to and do give physicians new-use efficacy information that has not been reviewed by the FDA, then lower the barriers to that review, and give prescribers a broader range of clinically relevant information with reduced search costs and no loss of information quality.