

December 27, 2007

VIA OVERNIGHT DELIVERY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Comments on Proposed Regulations
Expanded Access to Investigational Drugs for Treatment Use
Docket No. 2006N-0062

I. Introduction

The Crohn's & Colitis Foundation of America ("CCFA") and Advocacy for Patients with Chronic Illness, Inc. ("Advocacy for Patients") appreciate the opportunity to comment on proposed regulations that would expand access to investigational drugs for treatment use. The CCFA is a nonprofit, volunteer-driven organization dedicated to finding the cure for Crohn's disease and ulcerative colitis (collectively, inflammatory bowel disease or "IBD"). Advocacy for Patients is a nonprofit organization that provides free information, advice and advocacy services to patients with IBD and other chronic illnesses. CCFA's members and Advocacy for Patients' clients will be directly affected by the proposed rule.

IBD affects more than 1.4 million Americans. Typically, the medications used to treat IBD have been FDA approved to treat another disease. This is the case with many chronic illnesses and it is not unusual for a drug to be approved for use in treating some other disease, most commonly rheumatoid arthritis. Physicians often prescribe the drug for what is called an "off-label" or "unlabeled" use. The problem with this is that insurers commonly refuse coverage of off-label uses when the drug is expensive and bring into play the absence of FDA approval as their argument for not covering the drug. This runs contrary to FDA guidance and court decisions. Strengthening the FDA's approval of access to investigational drugs for patients with serious or life-threatening conditions who lack other therapeutic options will help to persuade insurers to cover these medications. At the very least, these rules will facilitate patient access to medications that are medically necessary.

IBD can be seriously debilitating and even life-threatening. Because it affects absorption of nutrients and hydration, patients in a flare can experience malnutrition and dehydration, which in turn can be debilitating, at best, and life-threatening, at worst. There are IBD patients who are fed enterally and parenterally because they cannot tolerate solid food. When the feeding site becomes infected, enteral and parenteral nutrition become more difficult and sometimes impossible, and the condition becomes life-threatening. Thus, the availability of new treatments are of critical importance to patients with IBD.

We write to make three main points:

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- First, we urge the FDA to clarify that these new rules would apply not only to drugs that are not yet FDA approved for any use, but also to drugs that are FDA approved for one use and being investigated for another.
- Second, we support any tools that will lead to expanded access to medications that will improve the health and the lives of the patients we serve. Indeed, we suggest additional ways in which the FDA could broaden access to investigational drugs, such as easing the requirements pursuant to which individual physicians may apply for expanded use with generally available information about the drug so that physicians outside of major research centers can submit requests.
- Third, we ask the FDA to confirm the continuing validity of FDA Drug Bulletin, April 1982, Volume 12 Number 1, Pages 4-5 (set forth below), and to signify that FDA labeling is not intended to dictate what physicians prescribe and insurers cover. These minor additions to the proposed rule would be of tremendous value to patients with IBD and other chronic illnesses.

II. Comments

A. The FDA's Expansion of Access to Investigational Drugs Will Benefit Patients

First, we applaud the FDA's effort to expand the use of investigational drugs. When dealing with diseases like IBD, it often is critical to get the patient the newest treatments available when conventional therapies fail. Indeed, getting access to such medications may well save lives.

We do not object to the criteria pursuant to which investigational drugs will be available. Limiting such availability to patients in dire need, and situations in which no FDA approved drug or use is effective, is both intelligent and practicable. The definition of "serious disease or condition" borrowed from other sources is sufficiently broad to ensure that patients in dire need will qualify.

B. The FDA Should State That the Proposed Rule applies to Drugs That are FDA Approved, As Well As Used, For Different Diseases

Although this may be implicit in the proposed rule, we urge the FDA to expressly state that the rule applies not only to drugs that have not been approved by the FDA for any use, but also to drugs that have been approved for one use while another use is not yet FDA approved.

There is absolutely nothing in the FDA's proposed rule that precludes the regulations from being applied to so-called "off-label" or "unlabeled" uses as well as entirely unapproved drugs. We believe that the FDA intends to include off-label uses that are investigational, and this

makes sense because these drugs have been through the entire FDA approval process, albeit for a different use. The fact that these drugs already have been vetted for safety purposes should decrease the risk associated with off-label uses. We urge the FDA to make this intent express in the final regulations.

C. Submission Requirements Should Be Eased for Individual Physicians Making Applications for Expanded Use

Although the proposed rule seems to contemplate that an individual physician can apply for expanded use access on behalf of an individual patient, the requirements of such an application may be prohibitive. In particular, § 312.305(b)(2) requires submission of the drug's chemistry, manufacturing, and controls information; pharmacology and toxicology information; and a description of all testing and clinical procedures that have been undertaken – information to which most individual physicians will not have access. Since pharmaceutical companies cannot promote the use of investigational drugs, and may lack incentives to request expanded use on behalf of a single patient, it is unclear whether they will be willing to make requests or assist physicians to do so. Indeed, this forms part of the reasoning relied on by the FDA for attempting to expand individual patient access.

The proposed rule clearly contemplates that there may be requests on behalf of an individual patient. The question is how an individual patient can obtain expanded access if there is no industry sponsor and the physician either cannot make the sort of detailed request that § 312.305 contemplates. We are concerned that the requirements imposed by this section will prove too onerous to facilitate expanded access submissions on behalf of individual patients.

Similarly, the provision of § 312.305(c) making physicians "investigators" for purposes of part 312 will be daunting and extremely time consuming. The typical gastroenterologist not affiliated with a large teaching or research hospital will not be able to satisfy these requirements. This may have the unintended effect of rendering the proposed rule relatively meaningless for the vast majority of the patient population in the absence of an existing IND.

Indeed, most doctors may not know whether an IND exists or how to find that out. At the very least, we would suggest that the FDA provide publicly available training materials that would help individual patients and physicians to determine whether there is an IND for the drug in question, and how to obtain a right of reference to the IND. This sort of piggy-backing on an existing IND is the clearest way for individual physicians to comply with the submission criteria. However, we believe that most physicians will need significant training and information in order to avail themselves and their patients of this option.

In addition, we recommend that training materials and information should be made available to the general public in an easily-accessed format, perhaps on the FDA's website, so that patients and patient advocates can access the instructions for submitting an expanded access use. The proposed rule indicates that FDA intends to train sponsors and physicians, but the physicians we are concerned about are the least likely to have time and resources to attend

trainings or read detailed materials. It is important, therefore, that patients and patient advocates be made aware of the opportunity to submit a request for expanded access use, and the requirements for doing so, so that they can inform their physician of this opportunity in compliance with the submission requirements of the proposed rule.

Finally, proposed § 312.310 sets forth additional requirements for submissions related to individual patients. Again, if the physician is at a center of research, or can easily access physicians involved in research, these requirements make sense. However, for the majority of treating physicians, these requirements are insurmountable.

We applaud the provision of procedures for emergencies in § 312.310(d) of the proposed rule. Even more, we strongly believe that § 312.315's procedures for seeking expanded access use when several individual requests are submitted on behalf of a small patient population may address some of our reservations. Still, we are concerned that patients whom the FDA intends to benefit from the proposed rule will be precluded from doing so due to the submission requirements applicable to individual patients will be impracticable for the majority of physicians.

In short, although we strongly support the goal of increased access for individual patients, we are concerned about the burden the proposed rule places on individual physicians who wish to obtain approval of expanded access for individual patients. Although we understand and support the FDA's safety-related concerns, we know that not all physicians have the support necessary to meet the submission requirements. The proposed rule may improve on the status quo, but we are concerned that it may not have done so sufficiently to increase access for individual patients. We urge the FDA to consider ways in which the submission process could be eased further for individual patients of physicians at non-research facilities.

D. The FDA Should Expressly Reaffirm Its 1982 FDA Drug Bulletin, Clarifying That Its Labeling is Not Intended to Dictate Insurance Coverage Decisions

When the FDA approves a drug or device, it does so based on the use(s) that the manufacturer has proposed to the FDA. However, physicians often prescribe the drug or device for a different use. This is entirely legal, as the FDA said 25 years ago. However, the absence of FDA approval for a specific use is used routinely as an excuse by insurance companies to refuse to cover drugs and devices for other uses, including routine uses, of expensive drugs and devices (although not for less expensive drugs or treatments). This has created a great burden – in some cases, an insurmountable burden – on patients who cannot obtain the prescribed medication without coverage by an insurer.

In *Weaver v. Reagen*, 886 F.2d 194, 197 (8th Cir. 1989), the court explained that “FDA approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient.” *Id.* at 198. The court quoted the text of an FDA bulletin as follows:

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners. Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug’s safety and effectiveness have been established and which the FDA has approved. These are commonly referred to as the “approved uses.” This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by the FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such “unapproved” or, more precisely, “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term “unapproved uses” is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to the FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.

FDA Drug Bulletin, April 1982, Volume 12 Number 1, Pages 4-5.

Based on this policy guidance, the *Weaver* court found “the fact that FDA has not approved labeling of a drug for a particular use does not necessarily bear on those uses of the

drug that are established within the medical and scientific community as medically appropriate.” 886 F.2d at 198. Thus, the court concluded that Medicaid could not limit the use of a drug to FDA approved indications.

This same rule does not now apply to commercial insurers. However, the unintended reliance on FDA labeling to justify denials of coverage has become routine as applied to new, expensive medications. Changes that the FDA makes to the status of investigational drugs or approved drugs for investigational uses may well encourage insurers to pay for investigational drugs or uses when the FDA imprimatur is present.

For example, Humira is a drug that was FDA approved for rheumatoid arthritis and is being used successfully to treat one form of IBD, Crohn’s disease. However, use of Humira to treat Crohn’s disease is not FDA approved. Many doctors are prescribing Humira for patients who have been unable to tolerate a similar treatment, Remicade. It is uncommon at best to find an insurer willing to pay for Humira, and the excuse for not doing so is that Humira is not FDA approved. With the new regulations, patients who are seriously ill or are experiencing a life-threatening flare of their disease will have a better chance at obtaining access to medication, or uses of medication, when all other treatments have failed.

Similarly, Xifaxan is FDA approved for traveler’s diarrhea, but not for the diarrhea associated with IBD. Physicians are finding that this medication helps with diarrhea caused by chronic bacterial overgrowth, which often accompanies IBD. When all other anti-diarrheal agents have been tried and failed, and the patient is wasting away due to refractory diarrhea, Xifaxan needs to be available.

Finally, although not confined to use by IBD patients, Actiq is a pain medication that is FDA approved for treating breakthrough cancer pain. The active ingredient in Actiq is Fentanyl, which is widely used to treat all kinds of pain. Yet, Actiq is not commonly available to patients with serious noncancer pain, even when that pain is totally disabling and all other pain medications have been tried and failed. Noncoverage decisions are based solely on the FDA labeling.

The FDA has a unique opportunity to reaffirm a position it took 25 years ago, that unlabeled or off-label uses restrict manufacturers’ marketing efforts, but not the ability of a physician to prescribe medications for such uses. To the extent that these off-label uses are considered investigational, the 1982 FDA policy guidance applies.

The FDA may be of the impression that the statute and regulations pertaining to use of investigational drugs should be sufficient to make this point. However, as the FDA itself has acknowledged, most doctors, and just about all patients, do not know that there is a procedure in place to access investigational drugs, and insurers use the absence of FDA approval as a rationale for declining coverage of these drugs. A clear statement that this is not the FDA’s intent would be most welcome.

The ability of a physician to prescribe a drug does not really expand access to that drug unless Medicare and commercial insurers will pay for it. If the FDA were to reaffirm the position it announced in 1982, making it clear that the FDA does not intend its labeling to provide a basis for an insurer to refuse coverage of an investigational drug, this would provide real, meaningful access to such a drug. In the absence of such a statement, FDA regulations that are intended to provide access to investigational drugs will be of little import because, in many cases, there can be no access in the absence of Medicare and/or commercial insurance coverage.

The FDA seems to assume that the sponsor of a clinical trial or investigation would provide the drug for free, and this may be the case at least some of the time. However, it is not generally the case, in our experience, that when an off-label use is being investigated, the manufacturer will provide that drug to individuals for treatment purposes. Indeed, pharmaceutical company patient assistance programs do not pay for off-label uses because marketing of off-label uses is not allowed. We urge the FDA to recognize that there can be no expanded access without consideration of the source of payment for the drug. That requires a direct statement that Medicare and commercial insurers should not use FDA labeling to dictate the scope of coverage.

One straightforward way to do this would be to amend the proposed rule to provide not only that it applies to investigational off-label uses, but also to state that drugs provided pursuant to, and in compliance with, this rule are provided with the approval of the FDA.

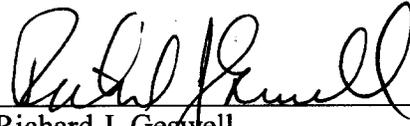
When the use of a drug meets all of the requirements of the proposed rule, the FDA is tacitly approving the use of the drug. If it simply would say so, that would greatly expand access to the drug because the only basis relied on by insurers for refusing to cover the drug would be eliminated.

III. Conclusion

Again, we appreciate the opportunity to comment on the proposed regulatory changes, and applaud the FDA's goal

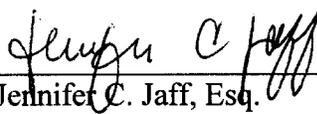
Of course, if we can be of assistance in your consideration of our comments, or in any other respect, we would be pleased to do so. Thank you.

CROHN'S & COLITIS FOUNDATION
OF AMERICA



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ADVOCACY FOR PATIENTS WITH
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