

# Off-Label Drug Use Needs Better Regulation

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Senior Editor

PHILADELPHIA — The Food and Drug Administration needs to change the way it regulates promotion of off-label drug use, according to the chair of the department of health policy and public health at the University of the Sciences in Philadelphia.

This year, the FDA issued draft guidance regarding off-label promotion. The draft guidance states that although any materials promoting off-label use must be peer reviewed, approval by the agency is not required, and the pharmaceutical company does not need to prove its intent to submit a new drug application for the off-label use, Robert I. Field, J.D., Ph.D. said at a meeting of the American Society of Law, Medicine, and Ethics. "This is considered to be a significant loosening of the requirements, certainly of the FDA's enforcement attitude."

However, the company must clearly disclose that the suggested use is off-label, and any published negative findings regarding the off-label use must be included in the materials. "The problem is, negative findings don't get published very often, so there's probably not going to be a whole lot of that," he added.

The comment period on the FDA's draft guidance ended several months ago; final guidance has yet to be issued. But there are certainly reasonable arguments for promoting off-label use under certain circumstances, according to Dr. Field.

Medicine only advances when information is shared, "and there are good reasons to allow off-label uses and therefore to allow physicians to know about those off-label uses," he said. "On the other hand, it is clear that lack of oversight will lead to overzealous, aggressive promotion of uses that have limited, if any, scientific substantiation. The big question [is whether the] average physician, who's working 80 hours a week [is] really going to be able to evaluate this information, even if it has a disclosure written at the top?"

Although the ultimate goal should be to get approval for an off-label use, pharmaceutical companies don't have many good reasons to do so, Dr. Field noted. "The problem is that clinical trials take a lot of time and the FDA is an overburdened agency; its reviews are slow."

Off-label use is abundant and has grown over the last 3 decades, Dr. Field said.

Before 1997, the FDA opposed all off-label promotion. The agency allowed limited distribution of peer-reviewed articles in direct response to physician requests.

In 1997, Congress passed the Food and Drug Administration Modernization Act, which allowed pharmaceutical companies to initiate distribution of articles promoting off-label use if they came from a legitimate peer-reviewed source, such as a journal or book chapter, and they could sponsor continuing medical education if it was done through a third-party operation.

But there were restrictions on these uses—the material to be distributed first had to be given to the FDA for approval, and the company had to intend to submit a new drug application for the off-label use.

In 1998, the Washington Legal Foundation sued the FDA, arguing that the restrictions on article distribution were unconstitutional under the First Amendment. The court said the agency could limit article distribution but could not require prior submission of the materials for FDA approval or require that the company intend to submit a new drug application. A similar lawsuit in 1999 produced the same result.

These rulings "left questions as to what would and wouldn't be allowed" under the act, Dr. Field said. Other challenges to off-label promotion rules were not as successful. In 2004, Pfizer Inc. was fined \$430 million for paying physicians to promote the off-label use of gabapentin (Neurontin) with little evidence of benefit. And a psychiatrist was arrested in 2006 for accepting \$100,000 to promote off-label uses for Jazz Pharmaceutical Inc.'s sodium oxybate (Xyrem).

**'The big question is whether the average physician, who's working 80 hours a week, is really going to be able to evaluate this information.'**

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Table 10:  
Percent of RA Patients Reporting Adverse Events  
in Controlled Clinical Trials\*

Event	Placebo Controlled		Active Controlled (Study III)	
	Placebo <sup>1</sup> (N = 152)	ENBREL (N = 349)	MTX (N = 217)	ENBREL (N = 415)
Injection site reaction	10	37	7	34
Infection (total)**	32	35	72	64
Non-upper respiratory infection (non-URI)**	32	38	60	51
Upper respiratory infection (URI)**	16	29	39	31
Headache	13	17	27	24
Nausea	10	9	29	15
Rhinitis	8	12	14	16
Dizziness	5	7	11	8
Pharyngitis	5	7	9	6
Cough	3	6	6	5
Asthenia	3	5	12	11
Abdominal pain	3	5	10	10
Rash	3	5	23	14
Peripheral edema	3	2	4	8
Respiratory disorder	1	5	NA	NA
Dyspepsia	1	4	10	11
Sinusitis	2	3	3	5
Vomiting	-	3	8	5
Mouth ulcer	1	2	14	6
Alopecia	1	1	12	6
Pneumonitis ("MTX lung")	-	-	2	0

\* Includes data from the 6-month study in which patients received concurrent MTX therapy.

<sup>1</sup> The duration of exposure for patients receiving placebo was less than the ENBREL-treated patients.

\*\* Infection (total) includes data from all three placebo-controlled trials. Non-URI and URI include data only from the two placebo-controlled trials where infections were collected separately from adverse events (placebo N = 110, ENBREL N = 213).

In controlled trials of RA and psoriatic arthritis, rates of serious adverse events were seen at a frequency of approximately 5% among ENBREL- and control-treated patients. In controlled trials of plaque psoriasis, rates of serious adverse events were seen at a frequency of < 1.5% among ENBREL- and placebo-treated patients in the first 3 months of treatment. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL, malignancies (see **WARNINGS: Malignancies**, **ADVERSE REACTIONS: Malignancies**) and infections (see **ADVERSE REACTIONS: Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed in RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis clinical trials are listed by body system below:

Cardiovascular: heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis, thrombophlebitis

Digestive: cholecystitis, pancreatitis, gastrointestinal hemorrhage, appendicitis

Hematologic/Lymphatic: lymphadenopathy

Musculoskeletal: bursitis, polymyositis

Nervous: cerebral ischemia, depression, multiple sclerosis (see **WARNINGS: Neurologic Events**)

Respiratory: dyspnea, pulmonary embolism, sarcoidosis

Skin: worsening psoriasis

Urogenital: membranous glomerulonephropathy, kidney calculus

In a randomized controlled trial in which 51 patients with RA received ENBREL 50 mg twice weekly and 25 patients received ENBREL 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalus, seizure, and stroke. No serious adverse events were observed in the 25 mg arm.

### Adverse Reactions in Patients with JIA

In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients (see **WARNINGS** and other sections under **ADVERSE REACTIONS**). Differences from adults and other special considerations are discussed in the following paragraphs.

Severe adverse reactions reported in 69 JIA patients ages 4 to 17 years included varicella (see also **PRECAUTIONS: Immunizations**), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, Type 1 diabetes mellitus, and soft tissue and post-operative wound infection.

Forty-three of 69 (62%) children with JIA experienced an infection while receiving ENBREL during three months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.

The following adverse events were reported more commonly in 69 JIA patients receiving 3 months of ENBREL compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient-year), nausea (9%, 1.0 events per patient-year), abdominal pain (19%, 0.74 events per patient-year), and vomiting (13%, 0.74 events per patient-year).

In open-label clinical studies of children with JIA, adverse events reported in those aged 2 to 4 years were similar to adverse events reported in older children.

In post-marketing experience, the following additional serious adverse events have been reported in pediatric patients: abscess with bacteremia, optic neuritis, pancytopenia, seizures, tuberculous arthritis, urinary tract infection (see **WARNINGS**), coagulopathy, cutaneous vasculitis, and transaminase elevations. The frequency of these events and their causal relationship to ENBREL therapy are unknown.

### Patients with Heart Failure

Two randomized placebo-controlled studies have been performed in patients with CHF. In one study, patients received either ENBREL 25 mg twice weekly, 25 mg three times weekly, or placebo. In a second study, patients received either ENBREL 25 mg once weekly, 25 mg twice weekly, or placebo. Results of the first study suggested higher mortality in patients treated with ENBREL at either schedule compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL (see **PRECAUTIONS: Patients with Heart Failure**).

### Adverse Reaction Information from Spontaneous Reports

Adverse events have been reported during post-approval use of ENBREL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ENBREL exposure.

Additional adverse events are listed by body system below:

Body as a whole: angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain

Cardiovascular: chest pain, vasodilation (flushing), new-onset congestive heart failure (see **PRECAUTIONS: Patients with Heart Failure**)

Digestive: altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation

Hematologic/Lymphatic: adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia (see **WARNINGS**)

Hepatobiliary: autoimmune hepatitis

Musculoskeletal: joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus

Nervous: paresthesias, stroke, seizures, and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis (see **WARNINGS**)

Ocular: dry eyes, ocular inflammation

Respiratory: dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder

Skin: cutaneous vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pruritus, subcutaneous nodules, urticaria

**Rx Only. This brief summary is based on ENBREL prescribing information v. 33: 03/2008**

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