The Off-Label Conundrum

Off-label use of biologics is increasing as treatment successes, patient demand, and new indications grow. While scientific evidence and medical opinion still guide usage, high costs, unknown side effects, and legal ramifications are primary concerns for payers, physicians, and manufacturers. **BY KATHERINE T. ADAMS,** *Senior Editor*

When the U.S. Food and Drug Administration issued new rules for prescription drug labeling in January, some of the thinking behind it was that if their physicians prescribed a drug for an unapproved indication, patients would be more likely to question such use.

Why would they, though? People with cancer — who compose the largest subset of patients who use biotech therapies — want results at all costs, even if for just a few more months of life. Other biotech therapies, particularly anti-inflammatory medications, show real promise in addressing a variety of previously undertreated conditions not now indicated on their labels.

To answer "why," look to Medicare, for starters. With Part D regulations quite specific about how off-label uses are covered, a patient could otherwise be stuck with the bill for a very expensive therapy. It remains to be seen if commercial third-party payers, who generally have been open-minded about off-label use of biologics when there is literature to support it, will begin to sing from Medicare's hymnal about when to bless such usage.

Look also to federal agencies. The FDA and the Office of the Inspector General have been aggressive in going after manufacturers' practices they perceive to be tantamount to promoting off-label uses.

Look to the legal system, though this cuts two ways: Patients can sue

"Much off-label use comes from physicians and specialists talking to each other, working with their societies, and attending national conferences," says Edmund Pezalla, MD, MPH. "And so we tap into their networks. That — not the pharmaceutical companies — drives use."

PHOTOGRAPH BY MICHAEL JUSTICE

SELECTED COMMON OFF-LABEL USES OF BIOLOGICS		
Agent	**Approved indication**	**Uses**
Adalimumab (Humira)	Rheumatoid arthritis	Psoriasis, ulcerative colitis
Becaplermin (Regranex)	Diabetic foot ulcers, wound care	Venous leg ulcers, scleroderma, sickle cell disease
Bevacizumab (Avastin)	Metastatic colon cancer	Wet age-related macular degeneration, late-stages breast cancer, lung cancer, kidney cancer
Cisplatin (Platinol)	Bladder, testicular, ovarian cancer	Thyroid and lung cancers
Efalizumab (Raptiva)	Psoriasis	Granuloma annulare
Etanercept (Enbrel)	Psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis	Behcet's disease, sarcoidosis, wound ulcers, vasculitides, pyoderma gangrenosum
Ibritumomab tiuxetan (Zevalin)	Non-Hodgkin's lymphoma	Various cancers
Infliximab (Remicade)	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis	Kawasaki's disease, psoriasis, Sjogren's syndrome
Oxaliplatin (Eloxatin)	Metastatic colon cancer, pancreatic cancer	Post-surgery drug regimens, newly diagnosed colorectal cancer
Rituximab (Rituxan)	Non-Hodgkin's lymphoma, rheumatoid arthritis	Skin malignancies, blood cancers
Sunitinib (Sutent)	Gastrointestinal stromal tumors, advanced kidney cancer	Breast, colon, and pancreatic cancers (in clinical trials)
Trastuzumab (Herceptin)	Metastatic breast cancer	Early-stage breast cancer
SOURCE: BIOTECHNOLOGY HEALTHCARE ANALYSIS		

if off-label use results in an injury — or they can sue if they are denied the best treatment available, a fact that is well recognized by physicians, payers, and the biotechs.

Labeling changes or no, off-label prescribing is an important part of the practice of medicine and the evolution of care, which means that the FDA cannot rule on the appropriateness of treatment. "Our current dilemmas are about the need for healthcare to incorporate uncertainty as well as a bias toward medical evidence," says Edmund Pezalla, MD, MPH, vice president and medical director of Prescription Solutions. "There needs to be an emphasis on good evidence when making coverage decisions, but plans also need to leave enough room for decision making in special cases."

With the biotech pipeline flush, the subject of off-label use is likely to become more important — and more touchy — not just because of their cost but also because, for now, few biotech drugs can show long-term safety data. "I would think that this would be of more concern because of the expense that the plan and members are incurring, and because there may be severe consequences that are not fully fleshed out," notes Sean Brandle, vice president at the Segal Co., a New York-based employer consultant. "That's what I would be telling our clients."

COST AND CONSEQUENCES

Last November, *Skin & Aging*, a journal for dermatologists, published an article that explored the off-label uses of 14 biologic agents for treat-

ment of dermatologic conditions. Tumor necrosis factor inhibitors adalimumab (Humira) and etanercept (Enbrel), and monoclonal antibodies infliximab (Remicade) and rituximab (Rituxan), were listed as effective in treating various skin cancer and inflammatory conditions, despite lacking indications for them.[1]

"Residents get exposed to off-label usage," says Francisco A. Kerdel, MBBS, BSc, chief of dermatology at Miami's Cedars Medical Center, and a coauthor of the article. This is particularly true, he says, in dermatology, "where we have rare conditions for which no effective therapy has been available. The new biologics can treat these conditions in a very effective manner."

Effective as though these drugs may be, trial data about off-label uses are generally limited. For example, women taking trastuzumab (Herceptin) have been followed for an average of only 2.5 years. Yet, their success is a magnet for more experimentation. Trastuzumab is known to be prescribed off-label for nonmetastatic breast cancer, a development that has generated at least as much hype as scientific evidence of its effectiveness.

"We follow clinical trial data rather than the label, so there are cases where a drug will have some pretty good evidence" to support off-label use, says John Watkins, RPh, MPH, director of pharmacy formulary development at Premera Blue Cross, in Mountlake Terrace, Wash.

In an interview with BIOTECHNOLOGY HEALTHCARE in February, Watkins singled out the use of rituximab to treat rheumatoid arthritis (which at the time was still an unapproved indication; since then, the FDA has granted Genentech an RA indication for rituximab). "We know the data are there," he said at the time, "so we will approve its use based on those data."

In fact, Pezalla, at Prescription Solutions, estimates that at least half the pharmacy benefit manager's total reimbursement load is for off-label usage. Prescription Solutions, like many formulary administrators, requires prior authorization for all specialty drugs. It also issues updated guidelines for off-label use on the basis of scientific evidence and accepted medical opinion.

"Our clients — employers and health plans who are paying for these medications — want the right

Three forms of off-label use

With biologics, off-label can mean three things: varying the dosage or dosing schedule, using the product for a condition for which it has no FDA indication whatsoever, or using it to address another aspect of a disease the drug is approved to treat.

Edmund Pezalla, MD, MPH, vice president and medical director of Prescription Solutions, gives an example of the latter. "We see a lot of interferon requests for suppressive therapy in hepatitis C, even though the initial therapy wasn't successful in eradicating the disease, in order to keep the infection in check."

Dosage variations come in different flavors. What Pezalla sees with rheumatoid arthritis or psoriasis treatments is that higher doses sometimes are used at induction of the drug, but that some patients are unable to come off the higher dose. "They go on the maintenance dose and then relapse. Then they go back to the induction dose and get better again. So, we have to work with the physician on what's actually happening with that particular individual."

The drug label, Pezalla explains, is based on the averages from clinical trials. "You'll see things written like 'A dose of 50 mg is no better than a dose of 25 mg.' Well, yes, on average. But there are probably a few people out there for whom the higher dose is the only way to go."

With infusibles, costs rise and fall with dosage changes, sometimes because the dosage is more creative. "We see unsupported off-label use with dosing parameters that are exorbitant. You will get someone who tries to justify a low dosage of something that is not supported in the literature — but often, you see a higher dosage," says Dave Willcutts, CEO of Minneapolis-based Ancillary Care Management. "The interesting thing is that once you start tightening the parameters, you don't see the doses come down. [The physicians] stop prescribing the drug altogether."

Off-label usage related to nonapproved indications is common in pediatric practice where an adult medication or dose may be prescribed for a child. In most such cases, although a particular drug may not have been shown to be effective in children or for a particular age group, there may be no other options, says Pezalla.

[1] Available online at: «http://www.hmpcommunications.com/SA/displayArticle.cfm?ArticleID=article4869».

people to get the medications, but they also want to make sure that they don't overspend in one area because they need to deliver health care to the whole group," says Pezalla. Some clients, Pezalla notes, try to limit their exposure this way by refusing to cover off-label uses of any kind.

At Regence Blue Shield of Idaho, Terry Killilea, PharmD, vice president of pharmacy, says "We rely on that overused term *evidence-based*." When determining whether an off-label use qualifies as a covered benefit, Killilea says, the questions to be asked are: *Is it a good trial? Can we perform the classic evidence-based analysis?*

"If they've done only two trials and have not shown benefit through the appropriate statistical strategy, then they have not documented benefit in patients," says Killilea. "If there are no data confirming value, you can't just assume value."

Still, Regence doesn't completely discount limited trial information. If there are only small trials, then you enter a subjective world where cohort studies and published case reports have to be evaluated to determine potential benefit. "It's difficult, because if you're going to stick to evidence-based data, you need evidence of benefit," says Killilea.

Dave Willcutts, CEO of Minneapolis-based Ancillary Care Management, which manages infusion services for payers, sees off-label use of infusibles as a growing area for concern. "The longer these products are out, the more they will be used off label," Willcutts says. To control costs, Ancillary Care Management has a grid system that tracks infusible use by three categories: FDA indication, off-label use supported by the literature, and off-label use not supported. How a center ratchets up its off-label use, says Willcutts, determines where they fit into the grid.

"If you look at something like IV gamma globulin [IVIG], where off-label use is significant, the number of conditions not supported by the literature that [nonetheless] drive a physician to prescribe the therapy is very high. If it's not controlled, it can represent a significant portion of someone's IVIG spend."

It remains to be seen if commercial third-party payers, who generally are open-minded about off-label biologics' use if the literature supports it, begin singing from Medicare's hymnal about when to bless such usage.

With time, what is and isn't acceptable changes, Willcutts adds. "You saw that with Enbrel being used off-label for Crohn's, until the literature came out and said 'Nope, it actually doesn't work for that,' and now [that use] has fallen off."

THE CANCER ARENA

Perhaps because many cancer patients have few viable treatment options, oncology is like no other field of medicine in terms of therapeutic experimentation — and the resulting knowledge of what appears to work and what doesn't tends to circulate quickly through the tightly knit oncology community. The National Comprehensive Cancer Network estimates that as much as 75 percent of biologics prescribing in cancer care is off label, and more than 100 trials for all kinds of cancers and off-label treatments are in progress. Chemotherapy itself came about as an off-label use of mustard gas derivatives in the 1940s.

"Oncology moves much faster than its literature," says Pezalla. "Most members who request coverage already have gone through the first, second, and sometimes third-line therapies, whether they are standard chemo, surgery, or radiation therapies. So, we have developed our guidelines to be as flexible as possible and to allow reasonable use.

"At the same time, our clients don't want us to approve the use of drugs that have no evidence in the literature, have been shown to be ineffective, or basically are experimental."

Surging costs and short-term benefit continue to top his clients' lists of concerns. Although the number of deaths per 100,000 cancer patients has fallen by about 9 percent since 1993, the cost of treatment is up 75 percent since then, with 60 percent of cancer drugs being used off-label. The annual price of trastuzumab therapy is about $48,000; colon cancer treatment involving several biologic and conventional drugs can cost $250,000 annually.

You might expect that federal policy regarding Medicare Part D coverage of off-label uses of biologic therapies would trouble oncologists — and you would be right. Under the Part D benefit, Medicare will pay

for off-label usage only if it is cited in 1 of the 4 FDA-approved drug compendia. Drug plans do not have the authority to cover any use not specifically listed in the compendia.

Mark Ratain, MD, professor of medicine and director of the Advanced Solid Tumor Clinic at University of Chicago Hospitals, thinks unit cost and reimbursement aren't as important as cost-effectiveness. He suggests using a metric, like comparing a specific off-label procedure with a year of dialysis, to determine how cost-effective a use is. "Though clinical trials of off-label usage have been limited, the data that are available are still valuable," says Ratain, "and most oncology drugs have survival metrics associated with them."

SAFETY ISSUES

As cost is a prime consideration, so too are safety and unwanted side effects. Killilea, at Regence, says significant side effects always must be taken into account. "When you look at an evidence-based review, you have to look beyond the number needed to treat, or NNT, which represents how many people you need to treat to show a benefit — say, 1 out of 20. You also look at the number needed to harm, or NNH, which is how many patients you treat before you see side effects. It's not a cost equation. I would say potential side effects are as important as, if not equal to, cost aspects."[2]

Kerdel, at Cedars Medical Center, agrees that experimentation should not be without regard for patient safety. "If you use a drug off-label, you shouldn't expect more serious side effects than have been published for that given drug in the FDA-indicated manner," says Kerdel.

LEGAL EGGSHELLS

Legal issues surrounding off-label use are complex and involve more than the FDA. "There's the potential for a lawsuit under the False Claims Act, which might be an issue for a U.S. Attorney or the OIG," says Allen G. Minsk, JD, partner and chair of the Food & Drug Practice Team in the Atlanta-based law firm Arnall Golden Gregory. A False Claims Act case can arise when a physician or a pharmacist may fill a prescription for an unauthorized use, submit a form for reimbursement, and then be reimbursed for the unapproved use. A manufacturer that promotes off-label information for a reimbursable product could be found to have caused a false claim to be made.

Then there are product-liability considerations. "Let's assume that the biologics company promotes off-label use, the physician uses it, and the patient gets injured," says Minsk. "The patient is likely to sue everybody in the claim in an effort to obtain some settlement, such as recouping medical expenses."

The promotional practices of biotech and pharmaceutical manufacturers are under intense federal and state scrutiny now, and anything that smells like off-label promotion could land the manufacturer in a world of trouble. "Partly, it's a matter of Medicare and Medicaid expenses," he explains. The government wants to ensure that patients receive products for approved indications, "not those promoted off-label, which may not have gone through the regulatory process."

Whistleblowers know this, and these kinds of lawsuits are becoming more common. Last year, Genentech and Biogen Idec faced a whistleblower suit claiming that rituximab, which at the time had indications for non-Hodgkin's lymphoma, was being promoted as a treatment for arthritis (a use not approved until this year). Employees often file such suits, says Minsk. "It wouldn't surprise me to see more whistleblower cases."

Minsk cautions that the line between promoting off-label use and educating physicians about the uses of a drug often blurs. "When I promote a product," Minsk explains, "I'm giving a certain perspective with the hope that I may sell something. If I'm educating, I'm presumably giving as much information as I can so that the recipient can be as educated as possible. It's the difference between providing the highlights of a story versus describing it in its entirety."

The advice Minsk gives to his clients is that if there is legitimate benefit to an off-label use, then proceed through the regulatory channel to obtain FDA approval for that ise. If the regulatory approach is not taken and if no alternative therapy exists, then provide the physician and the patient with as much objective information as they need to make an educated decision.

The legality of off-label use will not disappear — not as long as the practice continues to lead to breakthroughs in medical care. It just faces a lot more scrutiny now that biotech makes the stakes bigger. BH

[2] Recombinant factor 7a (NovoSeven), an clotting drug approved for congenital hemophilia, has shown promise in treating cerebral hemorrhages, but has been linked to deaths, strokes, heart attacks, and other complications, as reported recently in *JAMA*. The package insert has been changed to include a warning about side effects in patients without hemophilia.