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Warning: The Risks of Prescribing "Off-Label"

### BUSINESS OF MEDICINE

Our presidential election is only days away. Forty eight million people in America are uninsured and healthcare costs are rising two to three times faster than our nation's GDP. Where will America's healthcare system be in 5 years?

Welcome to ReachMD's monthly series focussed on public health policy. This month, we explored many questions facing healthcare today.

Some estimate that more than one out of every five drugs prescribed in the United States is for an off-label use. As doctors, it seems like we should be concerned about this issue, yet I am not sure no one are prescribing drugs off label.

You are listening to ReachMD XM 157, the Channel for Medical Professionals. Welcome to the Business of Medicine. I am your host, Dr. Larry Kaskel and joining me today Mr. Mark Herman, partner at the law firm of Jones Day and he defends drug and device companies in product liability cases, he also co-hosts a blog known as the Drug and Device Law Blog.

**DR. KASKEL:**

Mr. Herman, thank you for joining me.

**Mr. HERMAN:**

Thank you very much for inviting me. It's good to be here.

**DR. KASKEL:**

Mark what does it really mean or what's the legal term or interpretation when either a prescription drug or medical device is described as off-label?

**MR. HERMAN:**

Off label is any use that is not indicated in the package insert. So if you prescribe a drug for a different disease than the insert says it is indicated for or a different patient population, it is indicated in adults but you prescribe it in a pediatric patient or a different route of administration or dose or frequency, it is an off-label use. It is important to know off-label use is entirely legal. Doctors are allowed to prescribe drugs for any appropriate use. The FDA does not control the prescription of drugs, but manufacturers are not allowed to promote drugs for off-label use. So the doctor can use it for that use, but the manufacturer cannot encourage the use.

**DR. KASKEL:**

That is why when I have a drug rep in my office and I asked them a question, they now say I cannot answer that; that is off label.

**MR. HERMAN:**

They typically say they cannot answer it and they are permitted to put you in touch with typically physicians on staff with the drug company, who are allowed to answer it, but the drug reps cannot promote off-label uses.

**DR. KASKEL:**

It is so, what I am hearing is that I am okay in changing the dose on a medicine if I believe that that is in the patient's best interest and it is off label, but I am allowed to do it.

**MR. HERMAN:**

Yes, as a legal matter that is absolutely true.

**DR. KASKEL:**

Unless something goes wrong.

**MR. HERMAN:**

Well, if something goes wrong, you are likely to be sued and the fact that it was off-label, it is likely to come up in the case, but as a legal matter, you are entitled to make the off-label prescription.

**DR. KASKEL:**

And we are doing that every day I think in our offices. I mean there are constantly doctors saying oh you know try this, I usually use this dose, and I try this, and I try that, and they are completely off label, and we do it, and I do not think we think twice about it.

**MR. HERMAN:**

It is certainly very, very common. That is you said in the lead that it was about 20%, I have seen estimate saying that from 25% to 65% of all prescriptions are off-label; and in certain specialties <\_\_\_\_\_> oncology, the numbers are up at 65% or more prescriptions being off label, at least early in AIDS treatment and maybe still today, just about all patients were getting at least one off-label prescription, so it is hugely commonly place. Whether or not the doctors know that a particular prescription is off label, I will defer to you that is I do not know what doctors know about labelled indications and that might vary by specialty, by whether it is a drug or device, but certainly it is happening all the time. It is an absolutely routine to have off-label prescriptions.

**DR. KASKEL:**

When I think of off label usage, I think of Neurontin because that is the one that made all the headlines and doctors were using that for treating everything from seizures to you know ingrown toenails and that drug company got in trouble. Did the doctors get in trouble for going along with what the company was telling them to do at that time?.

**MR. HERMAN:**

I do not know how many lawsuits were filed against the doctors in that case. So I can't tell you what the answer is, but the question of course is different for the doctor than it is for the drug company. For the doctor, the question is did you meet the standard of care, and for the drug company, at least in the criminal case, or the case brought by the FDA, the question is, did you promote the drug for an off label use? So, different alleged seen, and you could have a different result in the lawsuit.

**DR. KASKEL:**

I would like to continue with the line of questioning counselor, in terms of what I should do to minimize my exposure when I am writing something off label. Should I tell the patient? should I have them fill out informed consents, and if I am doing all that, the patient is going to be a little skeptical and hesitant to perhaps do what I am telling them to do?

**MR. HERMAN:**

The first question is what you should do and the answer is of course meet the standard of care, if the label indication is the standard care, use the labelled indication, and if an off-label use is the standard of care, then use the off label indication, because you are thinking about the patient and you have to do what is best for the patient. The problem is if you prescribe it off label and something goes wrong and there is a lawsuit, what happens then, and the difficulty is that if the plaintiff can come up with an expert witness who says that your off-label prescription fell beneath the standard care, then you have your expert witness saying that you met the standard of care, but they have their expert witness saying that you fell beneath the standard of care and they have the package insert that they would put in front of the jury showing that look it is not even an approved use, how could the doctor who have done it? So they have that little added bonus if they come after you in a malpractice case of being able to point to the package insert in addition to the expert's testimony.

**DR. KASKEL:**

Let us move on to a medical device. I do not particularly prescribe a lot of them, but I am curious how you would use a medical device off label?

**MR. HERMAN:**

Sure, in the case that went to the Supreme Court involved a cardiac catheter, it was not indicated for use in patients with calcifications in the artery, but this patient had calcification. It was indicated a balloon catheter, was supposed to be inflated only to a certain pressure, and when that pressure did not work, the physician inflated it to a higher pressure. So, it is off label and that it is not an indicated patient population and it is not an indicated route of administration, and then of course, the patient has an ill effect, which has what prompted the lawsuit.

**DR. KASKEL:**

And in that case, what was decided?

**MR. HERMAN:**

In the context of devices for that type of medical device, the manufacturer was entitled to preemption defense, so the manufacturer could not be sued. The physician could be sued and the question in the case against the physician would be whether or not he met the standard of care. I am fairly confident there was a lawsuit against the physician, but do not know what the result of that was.

**DR. KASKEL:**

And how does it work with manufacturers in terms of getting approved by the FDA? Do they all get approved by the FDA? Do they have to all be approved by the FDA?

**MR. HERMAN:**

Yeap, the only way to sell either a prescription drug or a prescription medical device in the United States is to have the FDA approval.

**DR. KASKEL:**

And what if they want to get an off label use? Do they have to go back in front of the FDA?

**MR. HERMAN:**

Yeap, that is you start with no labelled uses, your drug, which say it is the that is drug is not even on the market, so you go through the whole testing process of laboratory tests and animal tests and preliminary safety tests and efficacy tests and then you get one labelled indication, then you are on the market for that labelled use, but either you see other possible usage or physicians using the drug, see other possible uses, and there are off-labeled uses out there in the world, either speculated about or actually being used, then the drug

company has to go back and do an entire new set of clinical trials to show that the drug is safe and effective for that new indicated use, and if it gets it, the FDA will add that use to the approved package insert.

**DR. KASKEL:**

But that is a very expensive, lengthy process you have just described.

**MR. HERMAN:**

You got it. You are talking about tens of millions of dollars in many years.

**DR. KASKEL:**

So do they do it or do they do not have to because they see that they are getting the business irrespective of having to do the trial?

**Mr. HERMAN:**

Both.

**DR. KASKEL:**

I mean does it become standard of care just by everybody doing it?

**Mr. HERMAN:**

It may. There are certainly some off-label uses that are standard of care, and for the drug company there are whole collections of things to think about on it. Sometimes, the drug company is already doing the clinical trials for the off-label use and it's standard of care when it is just the matter of the FDA reviewing the data and looking at it and finally giving you the indication and then what has already become standard of care becomes labelled. But there are other situations where drug company simply is not going to bother, getting the off-label use indicated. If it is a tiny little patient population, you are not going to spend 10 million dollars to one clinical trial to sell two doses of the drug and make 2000 dollars in profits. So it may simply not make sense to get a labelled indication for a drug.

**DR. KASKEL:**

I would like to go back to day-to-day operations and back to that question of informed consent. Do you see in any of your trials that a physician has actually sat down with the patient and had them sign an informed consent and that actually helped them in their defense?

**MR. HERMAN:**

The question of whether or not physicians had to disclose that they were prescribing off-label uses with a huge, huge spat back in the middle 1990s. Basically, every State that has spoken about it says that off-label use is not a required piece of the informed consent process. So it is the law currently is there is no legal obligations to tell patients that we are going to make an off-label prescription. There has recently been some scholarly literature that has suggested that that is incorrect and that physicians ought to tell patients if they are making off-label uses of drugs, but to-date anyway, no court has adopted that theory. If you wanted to, you could put it in your informed consent form or you could tell patients I am going to prescribe this drug, it is going to be off label and you would have to be very sensitive about how you explain that so that the patient was not scared away from taking the beneficial drug.

**DR. KASKEL:**

All right Mark, so it is in fact as you said that you know perhaps 50% of prescriptions are actually written off label, what is the point of the label that except I guess protect the drug company? Why call it labelled, why call it off label it is just 50/50?

**MR. HERMAN:**

Well, a federal bureaucracy is always going to be slower than physicians treating patients. You have somebody in your office you have to treat him. You cannot say stop. We are going to run clinical trials for 3 years and see whether or not this works. So there is no way that you are ever going to have labelled indications that precisely match what is going on in the practice of Medicine. The question that is what is the best regulatory scheme to have? What we have now is sort of a slower FDA and a faster practice of Medicine and you hope that those two schemes work in together provide topnotch care.

**DR. KASKEL:**

Are there better agencies in other countries around the world than the FDA.

**Mr. HERMAN:**

There are different agencies. Most developed countries have some type of agency that is passing judgment on drugs. Some of them approve drugs more quickly than the FDA, some of them more slowly. Whether or not that is good, of course depends on <\_\_\_\_> on whether or not the drug had any unexpected side effects. If the drug comes on the market quickly and is good and it is saving lives, then it was a good thing the agency act quickly, but if the agency acted quickly, put a drug on the market and then there were unexpected in severe side effects, the agency will be criticized for having acted too quickly. So there are.

**DICTATION ENDS ABRUPTLY.**