

LEGAL AND REGULATORY COMMERCIAL BATTLES

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Thank you. The topic today is the off-label use of medical products. Dr. Scarpace had mentioned that considering how much off-label drug prescribing actually really occurs, what's the real value of a label, right? The point is: the real value of an FDA approved label is that it provides another layer of regulatory and legal hurdles that the innovator company will use when they try to keep the generic company from launching their product. That's how it's used.

Unlike some of my other panelists, I'm not at all concerned on a personal level what the health impacts of these situations are or of the economics of these different situations. I'm only concerned with the legal and regulatory commercial battles that happen with respect to these medical products because the amount of money that's potentially involved is very, very large. Not only are the innovator companies concerned with it, the generic companies are also concerned with it, and even the investment community is often highly interested in what's going on.

Just a quick disclaimer. As an attorney I just want to put this out here. You know, there's no other legal advice today, obviously no confidential or proprietary information is being disclosed. The thing about confidential information is the investment community is very concerned in terms of compliance issues. They should be very concerned, they don't want to speak to doctors who are participating in clinical trials who have access to material non-published information. So they always have to check and confirm that when I'm speaking with them I'm not using information that I don't have a right to use.

So here's the alphabet soup slide. These are some of the abbreviations we're going to be using today: ANDA, abbreviated new drug applications; API's, active product ingredient; BLA's, biologics license applications. Certainly BLA drugs tend to be

much more expensive than normal small molecule drugs. BLAs fall under the responsibility of CBER, which is the FDA Center for Biological Evaluation and Research. Even though you would think drugs like Avastin, ERBITUX, ENBREL, HUMIRA, ORENCIA, all are essentially large molecule situations, should be being handled by CBER because of just an allocation or responsibilities within the FDA, it's actually being handled by the other center, which is CDER, C-D-E-R.

For each one I just wanted to give you a small number of examples of the types of products that the FDA agency actually regulates. Even though some of these cancer drugs are actually being handled through the other part of the FDA, laws and the regulations that apply to them they are still the same. So in other words, there is still no regulatory pathway to get a follow on biologic approved. And then I just put down some representative drugs that have been handled by CDER. I put down some respiratory situations: ADVAIR, Serevent, Symbicort. Some gastrointestinal disorders, I put down a list of drugs. And mental health disorders too. The last one we're not going to spend any time on this, but CDRH, the Center for Devices and Radiological Health, they handle medical devices and laser skin treatments and all those situations.

So again, we're continuing on and learning about the abbreviations and the regulatory framework that we're immersing ourselves into. The biggest one here would be CP, Citizen's Petition. A Citizen Petition can be filed by either the innovator company or the generic company. It's a specific written request to the FDA to have the FDA take some very specific actions. You have to spell out in great detail your legal and regulatory basis as to why you have a right to sort of make this request for the action. You also have to convince them on the merits why it should be a good idea.

Hatch-Waxman sets the basic balancing act between getting generic products to the market faster, notwithstanding the fact that there are patents involved and that the actual clinical data that's been submitted to the FDA by the innovator company is still owned by the innovator company. So there're rights inherent in that data. I don't know how many of you have heard this expression about Paragraph IV patent challenges. This is essentially the heart of the matter. It happens all the time in pharmaceuticals for the branded drug. These Paragraph IV patent challenges, I list the two different provisions as to where

they're found, list the way the patent laws are.

Now, the thing that's more interesting, it's more closely related with today's topic, is section eight. Now, Section Eight statements are accomplished by petition practice at the FDA. What you're trying to get the FDA to do is to allow you to literally cut out certain text of the innovator reference listed drug, certain literal language, get that cut out of it when your corresponding product gets FDA approval. The reason that you want this cut out is if the language remained in there you would have to make a patent certification against that language or with respect to that language including the corresponding patent, and you would be subject to patent infringement litigation.

PHSA, that's just an example of how biologics are regulated by a different set of laws than normal small molecule chemistry drugs. SP is a suitability petition. That's a type of petition where, for example, if you wanted to carve out this little text from the FDA approved label, you being the generic applicant, or if say you want to go from a like a tablet formulation to a capsule formulation, you would need specific FDA approval to make those changes.

We quickly get into the laws of the FDA when we're trying to do this analysis. By far one of the most important provisions within the FDA is found at *21 United States Code §355*. It's extremely long, I don't know, twenty or twenty-five pages to print out, and it lays out in great detail what's required when you file a new drug application; what's required when you file an abbreviated new drug application; what's required with respect to the corresponding patent certifications; what's required with respect to the level of bio-equivalents that you need to establish. 355-J is the basic provision for ANDAs, A-N-D-A's. So a normal run of the mill ANDA would go through 355-J. There's sort of a different level of an ANDA which could also go through 355-B and sometimes that's referred to as paper NDAs.

Then the last bullet here is just an example of how when the applicant company wanted to change a formulation they needed official FDA approval to do that. Here's an actual example, if you look at the green text there. If the use that's covered by the patent that is in the label of the innovator company, the reference listed drug is not the use that you're trying to get, you can try to get the language deleted from the label and you don't have to make a patent certification against it. So what you try to do when you are working with this is you file Section Eight

statements. The Section Eight Statements of Non-Use are saying, “look, we want to get this drug approved, it’s a generic version of the reference listed drug, but I’m not going for the full set of approved indications or usage that the original reference list RLD has.”

And then how does patent law get into this? It’s an act of infringement to file either an NDA or an ANDA that has Paragraph IV patent certifications. It’s a technical act of infringement and it literally creates jurisdiction of the courts to handle the sort of emerging dispute between the generic company and the innovator company.

We’re not going to go through obviously, because it’s too detailed and it’s too small a print, but in the bright blue at the top it’s very clear: the ANDA filing company, they want to, through a suitability petition, get the FDA to allow them to make certain changes from what the label would be in their corresponding drug application. They’re going to fight hard for it because like I said before, everything in this whole area relates to commercially significant money disputes and big money is on the line. So for example when, PROTONIX was launched at risk, it had a major impact. “At risk” means before the patent infringement litigation was over, the generic version was launched by Teva that had a major impact at least for a while on the stock price of Wyeth. So now you can see how the investment community gets concerned.

If you’re a big pharma, if you’re the innovator company, you’re not going to take this lying down. You’re going to try very, very hard to fight these changes. And so, the innovator companies file citizen’s petitions which are trying to fight either a Section Eight Statement of Non-Use, that’s one example, or you could file a citizen petition that just wants to say that because of the specific chemistry of this particular reference listed drug it’s not even appropriate for normal ANDA processing. That’s an example of what they would request in a citizen’s petition. Another example could be: even if we agree that it’s susceptible to normal ANDA processing routes under the legal and regulatory framework, you need to submit additional clinical data to truly establish sameness or bioequivalents. Basically you’ve got to come up with all these arguments that, “Yeah, we agree in general this reference listed drug product should be covered by normal ANDA practice, but it’s so scientifically complicated that you can do your normal ANDA practice, but more data is needed than normally.”

That's how they fight potential changes in the generic company's proposed label that they're trying to get.

One benefit from the innovator company's point of view is usually this patent infringement litigation is going on at the same time. This can clearly create delays because sometimes the judge in the patent infringement litigations will actually stay the litigation pending the outcome of the FDA docket fight analysis.

Next, we'll get into a teeny bit of chemistry. This is a pain medicine, Skelaxin, it's extremely important for King Pharmaceuticals. The actual molecule itself, the actual active product ingredient is very, very old, it's from 1962. And there's a picture of it. It's a small molecule. There has been patent infringement litigation going on for at least four or five years in relation to Skelaxin and potential ANDA generic counterparts being launched. There's a January 29th, this year, decision from a judge in the Eastern District of New York, a federal trial court, that invalidated the two patents. And if we look at these, that's sort of the crux of the matter here. The original innovator company got labeling that included text related to this drug being used in connection with food intake. And the reason they wanted that in there is their corresponding two patents, which are right there, which are listed in the *FDA Orange Book*, require that as a claim element.

So back in January of 2002 the FDA essentially agreed with the innovator company and said you need to have invivo-fasting bioequivalent study to get your ANDA approved. More recently, and within the last seven or eight months, they denied two separate citizen's petitions, both from the innovator companies and because of licensing arrangements it's almost like they were two innovator companies that were combined. The innovator company wanted to keep on protecting this asset. They wanted to make the label more complicated and include more data related to DDIs, drug-drug interactions. And this argument was shot down, this was not accepted by the FDA.

Another aspect was they wanted to get invivo drug-drug interactions studies done, and again that was not required. So this was really an attempt to make the regulatory approval much harder and more complicated and in this case it failed. You've got to remember that, on the 20th of January of this year, the two key patents listed in the *Orange Book* were invalidated by the district court judge down in New York. If you're King Pharmaceuticals, you are fighting very, very hard to come up

with something that will keep these potential generic companies away from your product. This is a different product. This is Testim, it's a testosterone gel. You can see the little chemistry structure. Obviously it's a very old molecule, many other differently-listed drugs within the *FDA Orange Book* contain testosterone as the active product ingredient.

This is even more recent. This is February 27th of this year, this corresponding generic application is trying to do something relatively minor, like a minor change like have different excipients, different inactive ingredients. But if you are Oxylium Pharmaceuticals you're going to fight that. And that's indeed exactly what they're doing. The petition practice at the FDA relates to Oxylium trying to make the ANDA harder to approve.

COPAXONE, this is a very successful drug from Teva. Here, the shoe has been put on the other foot. Teva is normally the big generic company going after a Big Pharma; here Teva is actually the innovator company and it is fighting against other generic companies. This petition practice at the FDA is an ongoing situation and, in fact, the more commercially successful your drug is the more likely it is that, in addition to patent barriers and patent infringement, you will fight as hard as you can to make the entry into the commercial marketplace of the generic company to delay that as long as possible.

I set up a little website that actually has a small number of documents that relate to this analysis. The documents include the actual FDA approved labels for some of these drugs. It includes the January 20th decision from the Eastern District of New York that invalidated the two patents.

The structures again, it included the Skelaxin three different patents, one of them is from 1962 that shows you how old the API is. That shows you why the corresponding patents are relatively weak, right? The API itself has been out since 1962, so that means to convince the patent office to give two more patents, they're going to really finesse the waters.

Thank you.