Trends-in-Medicine

February 2003
By Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA: Reviewing New Drug Safety Issues

When FDA officials speak, people listen – or at least they should if they want to gain insight into the new drug approval (NDA) process. In an interview recently, a senior FDA official offered some perspective on how the agency deals with certain specific safety questions. Dr. Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs), also discussed the planned March 12-13, 2003, meeting of the Oncology Drugs Advisory Panel.

Drug Safety

Question: ***How does the FDA evaluate the safety of a drug where any potential safety issue is not likely to occur for 10, 15 or even 20 years?***

Dr. Temple: "Look at the animal data and any histopathologic changes…and if the issue looks like a class problem, you may well need long-term studies, which means more like two years. Then, look for signals, like QT, which used to be obscure, or CPK levels, which are now a possible indicator of rhabdomyolysis, so you can avoid doses that are a problem."

His longer answer to the question was that there are several things sponsors can do to assure the FDA of long-term safety, including:

Animal studies are critical.

Dr. Temple: "Your animal studies become more important in a case like that (when there is a long-term safety issue). If carcinogenicity is a concern, that is how we find out, for better or for worse. So far, all human carcinogens are also animal carcinogens. If the toxicity is something like that, you can do long-term animal studies for carcinogenicity. Things that take many years in humans show up much faster in animals… Animal data is critical. That is the standard for carcinogenicity -- or to tell if something is damaging to brain cells – and we pay close attention to animal studies for degenerative studies."

Pharmacology can be important, especially with class issues.

Dr. Temple: **"**It depends a lot on what you think is going on. If the abnormality is tied to basic pharmacology, you would be very nervous about other members of the class. For example, once we learned that a number of drugs intended to improve heart failure actually made people die faster, we developed a basic rule that said we won't approve drugs for heart failure unless we have outcome data that shows at least the drug is not doing harm, and ideally that it is doing good. So, in addition to symptomatic improvement (in heart failure), sponsors need to show no long-term adverse events. Those trials take a year, not 5 years.

"Similarly, the experience with anti-arrhythmic drugs has led to a situation where if you want to treat an arrhythmia symptomatically or if you want to prevent recurrence of atrial fibrillation (AF) – which doesn't kill you – we want evidence

you don't make things worse. So, dofetilide and sotalol were only approved recently, and luckily dofetilide had two large outcome studies (the DIAMOND studies), and we put them in the label. They were reassuring about overall survival. And sotalol many years ago had a study from a beta blocker post-infarct trial which showed about a 20% reduction in mortality. That wasn't statistically significant, and it didn't get that claim, but it was very reassuring."

Epidemiologic studies are not reliable.

Dr. Temple: "Obviously, it took a very long time and a very large study to learn that HRT is not very good for you. Fortunately, those drugs are not in my office, but obviously you have to think about labeling. HRT never had a claim for reducing cardiovascular events, but everyone thought it did, which is another reminder that epidemiology can be wrong…(But) sometimes you just have to do epidemiology despite its flaws. And sometimes you need to do more than one."

Long-term human studies are nice but often not realistic.

Dr. Temple: "A good question is how you get really good long-term data for a symptomatic drug? You can get it for lowering lipids because people stay on lipids a long time because they don't hurt. How do you get a placebo-controlled, long-term depression trial when we know that even in short-term depression trials, people drop out after four to six weeks if they are not feeling better? What you can do is compare two drugs, but if it is a problem with a whole drug class, you won't see a difference.

"The COX-2s are very interesting. Merck showed an unexpected increase in cardiovascular events, and we have to worry about how to decide if that is unique to Vioxx. It reminds us that drugs sometimes do things you didn't expect them to do. But, having known that, it is still difficult to know what to do.

"We are seeing more and more long-term studies of drugs that used to be in short-term studies. Now, weight loss studies are at least six months long and placebo-controlled. Does that pick up everything? It didn't pick up valvulopathy with (Wyeth's) Redux, but no one was looking for that. We would have had to think to do an echocardiogram, and we didn't think to do it before. Now, we are smarter, and we know about QT, so we won't approve drugs without QT evaluations…It is very hard to do long-term placebo-controlled studies, which are best, for drugs for symptomatic treatment because people won't put up with the placebo."

High-dose studies are important.

Dr. Temple: "We are much, much cannier about drug/drug interactions than we used to be, CPY450 interactions, etc. And we really want to know what happens when you push the dose by 10 times or high. Terfenidine (Hoescht's Seldane) didn't cause a problem until levels were increased 45 times or it was given with a CPY450 pathway drug."

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Why did you call this panel meeting?

Dr. Temple: "We thought it was a good time to review the experience (with accelerated approvals) and think about it. There is no question that a whole bunch of drugs got on the market sooner with this process than otherwise could have, just as we hoped. There was good clinical data on some, and some aren't done yet. Some were very difficult to get the actual clinical benefit trials. It's not that we hate the program or don't think it was a good idea to do it."

Are you thinking of ending the program?

Dr. Temple: "No, we think it has had substantial benefits. There are some differences in the way it happens in different places. A lot are in HIV, and in those cases, the study that gives you accelerated approval is almost always the same as the study giving final approval. The endpoints are the same – viral suppression at 26 weeks (which is not clinically meaningful) for accelerated approval and viral suppression at 48 weeks (which is clinically meaningful) for final approval. But it's still the same trial, and the accelerated approval rule says that what leads to the initial approval should prove clinical benefit."

"In oncology that is not true. Sometimes, sponsors do the first (accelerated approval) trial in refractory cancer, and then do a trial in earlier stage cancer to show clinical benefit (for final approval) because they think it will be hard to show clinical benefit if in very refractory stage patients. So, we've been reasonably content with that, but we want to show the data and think about this."

NOTE: *Here is what the FDA website says about accelerated approvals*: "The studies are designed to measure and the FDA evaluation is performed on the basis of a surrogate marker (a measurement intended to substitute for the clinical measurement of interest, usually prolongation of survival) that is considered likely to predict patient benefit. The approval that is granted may be considered a provisional approval with a written commitment to complete clinical studies that formally demonstrate patient benefit…"

Do you have any plans to withdraw any drug because the sponsor did not complete a required post-accelerated approval study or because a sponsor failed to show clinical benefit in a post-accelerated approval study?

Dr. Temple: "There is nothing on the table but that remedy is available to us. We haven't done it, but there are circumstances in which we would, but we are not going to the committee with that intent."