Inappropriate FDA Dismissal of Saphris® Cardiac Effects that can result in 'Sudden Death'

Drug induced prolongation of the QT interval on an electrocardiogram (ECG) can allow lethal cardiac arrhythmias to develop. These arrhythmias can cause the heart to suddenly stop pumping blood causing a person to simply keel over and die. This adverse effect is called *'sudden death'* and is a well known problem with antipsychotic drugs, although the degree of the effect and the risk of death varies with the antipsychotic. Saphris® has a very pronounced QT effect that is the second worse of all antipsychotics on the market. Even so the FDA apparently knowingly and willfully allowed Pfizer and Merck to use clearly inappropriate computer modeling to essentially claim in the labeling there was no QT effect at all and no increased risk of cardiac sudden death with Saphris. Consequently, physicians who are concerned about patients with heart conditions, which are common in patients with schizophrenia, may be more apt to prescribe Saphris® for these patients based on this apparently falsified labeling and unknowingly place them at an increased risk of dying.

During the development of Saphris® a dedicated clinical pharmacology study was performed to assess the risk of QT prolongation and sudden death with Saphris®. These studies were instituted because a QT prolongation issue was detected during the review of another antipsychotic developed by Pfizer, Geodon®. International regulatory agreements indicate that a drug that causes 5% of people to have a QT prolongation of 10 milliseconds or greater at any time after taking the drug has an increased risk of sudden death. This value is based on making sure you can detect a clinically important QT effect where the average QT prolongation is 5 milliseconds or greater. Generally these studies include doses higher than the doses approved to make sure that the effect in patients who have extremely high drug exposures are also covered. However this approach with simply increasing the dose is misleading with Saphris. This is because Saphris® is taken sublingually and as the dose is increased a greater percentage of the dose is swallowed and converted to different metabolites than when it's absorbed in the mouth with lower dosages. Thus the exposure to Saphris® increases less than proportionately to the increase in dose, whereas the exposures to Saphris's metabolites increase more than proportionately with the increase in dose. Thus if the QT effect, or a protective effect[1], is due to certain metabolites the QT effect cannot be correlated with Saphris® concentrations nor to the concentration of a single particular metabolite without information on all metabolites and how they affect the receptors known to cause QT effects.

A table summarizing the results of the QT study is attached. (See Exhibit 5.1.) The greatest QT prolongation occurs at 2 hours after a 10 mg dose with 5% of the patients having a QT prolongation of 17.1 milliseconds or greater. Additionally the average QT prolongation 2 hours after this dose is 10.5 milliseconds which is much greater than the 5 milliseconds which is the level thought to be predictive for sudden death. Ten milligrams is the dose prescribed for patients with mania, and this is not only a clearly clinically significant effect on the QT interval, it is a such a large effect, that if it were much higher

[1] Such a protective effect from a metabolite would be due to a blocking of QT effect from a separate metabolite.

Saphris® would be too dangerous to have on the market. In addition, there are clinically significant QT prolongations at every dose level from 5 mg to 20 mg at multiple time points after the dose. So the QT prolongation and risk of sudden death is clearly real and not just a fluke reading at a single time point.

Other points evident from the table are that there are two peaks for clinically significant QT prolongation at each dose level. Secondly, the time to the clinically significant first peak of QT prolongation ranges from 2-4 hours after the dose, and from 4-8 hours after the dose for the second peak. Third the degree of QT prolongation increases up to a dose of 10 mg and then decreases at 15 mg, and decreases even more at a dose of 20 mg. These observations are most likely explained by an interplay of effects from different metabolites that change ratios as a greater percentage of the dose is swallowed as the dose of Saphris® is increased.

The likelihood that the QT prolongation is due to metabolites is most clearly evident from the time of the first peak in QT prolongation being from 2-4 hours after the dose. As Saphris® is taken sublingually it's absorbed rapidly and the typical peak for Saphris® (asenapine) itself occurs between 0.5 and 1 hour after Saphris® is taken. This delayed response for the QT increase is most likely due to it being from metabolites that take time to form and accumulate, and is an example of pharmacodynamic disequilibrium which is a well known and common occurrence with drugs. The international regulatory standards that the FDA is a party to indicates that computer modeling of QT effect vs. drug concentration is not recommended, and it's precisely because of this and the potential effect of metabolites.

Leading up to the Saphris® review the FDA put in place a dedicated team to evaluate QT studies, and Saphris® was the first psychiatric drug where the QT team completely took over the evaluation of the QT effect. The pharmacometricians, Drs. Christine Garnett and Pravin Jadhav, ignored basic pharmacologic principles, used summary data instead of the data available, and then forced the summary data to be fit to a straight line model. These are major errors when doing computer modeling. You always let the data determine the model whether it's a straight line or some other type of relationship, and you should never predetermine the model and then force the data to fit it. Any pharmacometrician would certainly know this.

I have included a copy of the FDA pharmacometricians' computer fit of QT prolongation vs. concentration for Saphris® (asenapine) and the control drug Seroquel® (quetiapine). (See Exhibit 5.2.) Notice that below a certain drug concentration the fitted line falls below zero which is indicated by the red line with projected intercepts of -8 milliSeconds for Saphris® (asenapine) and just over -10 milliSeconds for Seroquel® (quetiapine). THIS IS IMPOSSIBLE. For when there is no drug in the body the effect on QT prolongation should be zero, and for the effect to be negative when there is drug in the body simply cannot be. Use of this type of modeling by the pharmacometrics group has likely caused a number of drugs to be

interpreted as having no clinically important QT effect at all even when there is a significant risk of QT prolongation and sudden death as with Saphris®.

My understanding is that this technique was developed by a pharmacometrician named Yaning Wang who has graduate degrees in pharmaceutics, statistics, and biochemistry plus an undergraduate degree in pharmacy. So he clearly should know that this sort of modeling is inappropriate and misleading, and could kill patients. When I first saw this with another drug I went to Dr. Wang and told him this was biologically impossible. His response was *"that's what the model says"*, yet he set up the model and programmed it. In contrast I was able to develop a non-straight-line model that not only fit the data but made perfect sense biologically. Yet the pharmacometricians have used this clearly erroneous and misleading model with a number of drugs and as a result have likely repeatedly endangered patients.

Even though this is the standard method that the pharmacometricians on the QT Team use to analyze QT data, this model was not used for the labeling of Saphris®. Instead Pfizer, who did the development of Saphris® developed a straight line model which produces an even flatter response and this model was used by Schering-Plough to justify the labeling. This model has all the same problems as the FDA pharmacometrician's model and then some and was used to calculate a predicted QT prolongation at asenapine's peak concentration which occurs well before the actual peak QT effect.

Due to the flatness of the equation's slope the calculated QT prolongation was so small that in essence it indicates that there is no risk of sudden death at all and this is reflected in the labeling. As this is clearly erroneous and endangers patients Saphris® appears to be misbranded, which would prohibit it from being introduced into interstate commerce by the Food Drug and Cosmetics Act. Additionally, I found that the data file that Schering submitted did not contain all the concentration data as evidenced by plots of the data in other parts of the submission. Consequently Pfizer's modeling could not be checked. This alone should have prevented any labeling claims based on the modeling.

Dr. Garnett and Wang's acceptance of linear modeling has been criticized in the scientific literature by a number of FDA statisticians. However separate from the published criticisms the clinically significant QT effect at multiple time points after the doses obviates the rationale for the linear modeling, plus the violation of critical pharmacologic assumptions means that the claims based on the linear modeling of QT effect with Saphris® are erroneous even if Dr. Garnett and Wang were correct in their statistical arguments. In my opinion the pharmacometricians should surely know that the methods used were inappropriate and would endanger patients.

In contrast to using methods that make it harder to show an adverse QT effect; around the same time the pharmacometricians were also involved in implementing new statistical methods that lowered the bar for

claiming that antipsychotics are efficacious. Consequently, not only may newer drugs be more dangerous than the labeling indicates but they also may not be as efficacious as older drugs.

The FDA's devotion of resources and emphasis on extensive statistical arguments by a person with a master's degree in statistics to dismiss the QT safety issue that may result in the deaths of patients, which was opposed by a number of FDA statisticians and by the FDA clinical pharmacologist who noted that basic principles of concentration effect relationships in pharmacology were ignored, stands in stark contrast to the FDA's suppression of any further examination or analysis of Saphris's lack of efficacy in mania, a major safety issue that effects approximately half of all patients who would take not just this drug but potentially any antipsychotic for this indication.

In November 2007, around the same time as the Saphris® QT review, Representative Rosa DeLauro, the Chairwoman of the House Subcommittee with responsibility for FDA oversight, issued a letter voicing concern about the Reagan-Udall Foundation's potential for facilitating the approval of drugs and devices based on lower standards for safety and efficacy and the involvement an ex-Industry VP, Shirley Murphy, heading the FDA Office of Translational Sciences (OTS) that might facilitate this. The Office of Clinical Pharmacology is under the Office of Translational Sciences and the OCP pharmacometrics group at the time was being run by another ex-industry VP from Pfizer, Bob Powell, who was apparently responsible for Pfizer's interest in pharmacometric modeling. He and his subordinates in the pharmacometrics group were intimately involved in the creation of the Reagan-Udall Foundation. He was also a VP at Glaxo when the head of OTS was a VP there. Prior to the Saphris® review, when Pfizer was still expected to be the sponsor, he would bring in Pfizer pharmacometricians to have all day social affairs with the FDA pharmacometricians. One of his FDA pharmacometricians falsified a presentation and also possibly a publication that were used to promote their agenda. Additionally the pharmacometricians would largely only work on items that would promote pharmaceutical industry drug development instead of doing reviews, and would bully and harass anyone who suggested that the group should do what they were supposed to do.

Recently the international standards on assessing QT effects have been updated to make it easier to use these modeling methods. Yet they contain huge loopholes that would allow additional misleading claims with drugs in the future. Plus Dr. Garnett, the pharmacometrician who reviewed Saphris's QT effect has been making presentations to the pharmaceutical industry on how such linear modeling can be used to dismiss QT effects when they are detected. As for Dr. Jadhav, the other FDA Saphris® pharmacometrician, in 2012 he left the FDA and joined Merck. This raises the question of whether his involvement with Saphris® facilitated this move.

As for Dr. Wang when I worked with him he was a foreign national. Consequently, if he (and possibly Dr. Jadhav, as well as the foreign nationals involved in the pyridostigmine approval) have since become US citizens I believe it's possible that they might have falsified answers to standard questions on their citizenship applications.

To Be Continued.