Charles Ho, Ph.D. Revised Aug. 31, 2005

Preliminary review on BLS using the SQUID magnetometer under NDA 21882:

My review is mainly on the engineering issues with the biomagnetic liver susceptometry (BLS) using the SQUID magnetometer.

Issues with Exjade NDA 21882:

1. The main issue is that the sponsor has ignored magnetic signals that originate from sources other than liver iron concentration (LIC). From IND 58554, the main pick-up coil of the SQUID magnetometer is a second order gradiometer aligned vertically inside the SQUID magnetometer dewar. This means that magnetic noise rejection is only effective in the vertical direction, and magnetic noise sources that are located off the vertical axis are not suppressed.

   Further, even a second order gradiometer does not have the resolution needed to distinguish between sources that are located just inside vs those just outside the liver. However, the sponsor's claim of measuring only LIC can be interpreted to mean that the device will not detect iron signals from the heart, spleen, blood, etc.-- this is not true with the present second order gradiometer arrangement, which has only limited spatial resolution in one direction.

2. The sponsor used sonograms to locate the specific location of the liver in each patient, since the exact location and size of each patient's liver is different. This information was only used to orient the patient so that the patient's liver inside the thorax was located directly under the tail of the magnetometer dewar. However, the sonograms were recorded in air while the patient was breathing normally. But the same patient was under up to 10 kg of water during the BLS measurements, and told to exhale and then hold his/her breath. (A small number of patients were told to inhale.) The sponsor has not adequately compensated for possible changes in the shape and/or location of the liver between these two procedures.

3. Further, the BLS measurement protocol is identical for each patient-- the same 8 cm downward movement of the patient's bed in 8 or 10 sec. Thus, how does the device take into consideration the different depth, size and orientation of each patient's liver?

4. The sponsor has tried to use a model to fit the data, but the model has the following limitations:

   a. The patient's liver is modeled as an ellipsoid with 3 axes. For example, a = 8.5, b = 8.0 and c = 3.0 cm. The real liver is definitely not this regular shape.

   b. Similarly, the thorax is modeled as a cylinder, but the cross section of the human thorax is not cylindrical.

c. The sponsor is assuming one susceptibility value for all iron inside the liver. This assumption has not been validated although iron has more than one oxidation state.

5. The raw data recorded by the SQUID magnetometer were first inspected by the device operator(s) before being accepted for entering into the study database. Such human intervention may render the data susceptible to selection bias.

On the other hand, in the IND 58554 study the sponsor provided calibration data using biopsied samples of liver tissue to show a linear relationship between detected signal magnitude and LIC--this was a situation in which magnetically noisy sources were minimized.

Further, data presented in the present NDA also showed some degree of correlation for BLS data using the same SQUID magnetometer. (See page 23 of Iron Burden Document.) However, as discussed above, I believe that the location of the iron inside the patient was not limited to the liver alone.

Lastly, although FDA/CDRH has cleared a certain SQUID magnetometer to market under a premarket notification process, that device does not include an applied magnetic field and is intended to measure magnetocardiograms only. It should be clearly understood that my present review does not confer any marketing authority to the SQUID magnetometer used in the present NDA, since there is neither premarket notification nor premarket application submission made to FDA/CDRH on the present version of the SQUID magnetometer.

Recommendations

Based on the above discussion, I believe that the sponsor has not proven the claim that BLS data are an accurate representation of the absolute value of LIC inside a patient.

I recommend that BLS data collected using the same SQUID magnetometer, for repeated measurements on the same patient under the same study protocol, have some value as a trending indicator proportional to iron load inside the patient, under the condition that the iron load be interpreted as residing inside an undetermined portion of the patient's body, and not limited to the liver alone.

Lastly, my recommendation does not confer any marketing authority to the SQUID magnetometer used in the present NDA study, since there is neither premarket notification nor premarket application submission made to FDA/CDRH on the present version of the SQUID magnetometer.