What Would Convince a Regulator

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Replacing TQT

We recognize that a full-fledged TQT study is costly and can even be difficult for toxic drugs, long half-life drugs, etc, i.e., when the relatively short crossover design won't work.

It seems reasonable to hope that an appropriate array of animal and phase 1 human studies could, at least in some cases, do what the TQT study is supposed to do; let you decide whether or not there is QT prolongation above "the level of regulatory interest."

And, of course, this is already perfectly possible, but

ONLY IF THE DATA SHOW PROLONGED QT, that is, a positive QT study.

So far, at least, we do not accept negative animal and/or phase 1 QT data as equivalent to (or having the effect of) a negative TQT (QTc effect < 5 msec, as indicated by upper bound of effect < 10 msec in a study with a reasonable active control).

Effect of Positive TQT

1. ICH E-14

   ICH E-14 really identifies only one: Much more attentive phase 3 ECG assessment, outlier analysis

2. Reality

   BUT, in reality, there's can be more implications, depending on the dose that gives a change in QT > 10msec, the magnitude of the increase, potential for drug-drug interactions, and the shape of the D/R curve

   - QTc effect > 20 msec at therapeutic concentration is very worrisome, although phase 3 data can mitigate
   - QTc effect 10-20 gets attention, increasing with size of the effect and with lots of attention to phase 3 and shape of D/R

     Thus, ziprasidone with an effect about 15 msec seemed to have a plateau QT effect despite higher doses and phase 3 showed no people > 500 msec

Can a C/R give the same clues (and does lack of positive control weaken it all)

Annual/Phase 1
Positive Vs Negative

We've said a positive C/R will serve as an indicator of QT prolongation and no TQT is needed.

I'm a little nervous that some of the other implications cited before will not be so well-described, especially if no positive control. That is

threshold – yes, you can be sure of this
details – no, at least maybe not

When could a negative effect be convincing?

So far, we've said only if the effect was actually QT shortening

What could broaden the use of a "negative" result?

Sensitivity/Specificity of Negative

Fundamentally, we would need assurance, provided by experience, that a combination of negative animal models (which to be determined) and the absence of a C/R for QTc (or conceivably a slope below some specified value), essentially always predicts a negative TQT outcome.

Considerations

1. N – To know you'd almost always get the right answer you would want an error (false negative) rate near zero with a reasonable sample (say > 50).
2. It's fair to ask whether all false negatives are equal.
   Maybe could tolerate missing 5-10 msec, but surely not greater
3. How critical is lack of positive control? If there are still no false negatives, maybe OK.
4. If C/R is reassuring, do animal data matter.
5. Can we say how high (multiple of therapeutic level) the study has to go? Do potential interactions or influence of renal/hepatic function alter this.