TQT: Impact on Clinical Development

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Disclosures

- Dr. Kowey has provided consultation regarding cardiac safety to multiple companies, including advice about the proarrhythmic potential of non-cardiac drugs.
- Dr. Kowey's financial arrangements are purely fee for service. He holds no equity interest in any pharmaceutical company.
- Dr. Kowey tends to be surly and impatient when dealing with QT issues, especially when the benefit greatly trumps putative risk.

Lawrence Peter Berra

"You can observe a lot just by watching."

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TQT: A “Thoroughly” Unique Opportunity

- Easily obtainable, highly recognizable biomarker
- The acquired disease mirrors the congenital form
- Linkage between an ECG parameter and a catastrophic outcome
- Risk roughly proportional to the magnitude of QT prolongation

Yogi Berra at His Best

"If I didn't believe it, I wouldn't have seen it."

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TQT: Clinical Development Benefit

- Quantitative answer (in most cases)
- Predictable pathway to labeling
- Workable methodology (once you get the hang of it)
- Appears to work to keep unsafe drugs off the market or at least labeled properly

Yogi

"If the world was perfect, it wouldn't be."

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TQT: Pitfalls

- The measurement isn't easy
- The methodology is not always applicable
- Limited consideration of pre-clinical information
- Enormous assumptions about pre-eminence of Cmax
- Cost that places a burden on development costs (esp for small companies).
- Defining the "supra-therapeutic" dose?
- Premature demise of new chemical entities
- Not all QT prolonging drugs carry risk
- Labeling fatigue

Yogi Again

"If you don't know where you're going, you might end up some place else."

TQT: Now What?

- We need better pre-clinical information that can be supplemented by a more reasonable clinical paradigm
- We also need better and more reliable post-marketing surveillance for real events
- We don’t need a monolithic approach that fails to account for the vast differences in chemical entities

Yogi, One More Time

"The future ain't what is used to be."

The Future

- Movement away from assessment of single cardiac currents (e.g. hERG)
- Discovery and consideration of multiple mechanisms of proarrhythmia
- Better use of in vitro/in vivo models with scrupulous standardization and validation (established via clinical events, not surrogates)
- Strategic use of intensive ECG methods
- Quantification of clinical events from new age data sets/analyses