It is interesting to note that a package insert for erythromycin includes information on QT interval prolongation in the Warnings section (173):

> **WARNINGS**.... *QT Prolongation.* **Erythromycin** has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

h. FDA's Decision-Making Process in Evaluating QT Intervals

FDA provides Sponsors with the opportunity to consult with the FDA's *QT Interdisciplinary Review Team* (QT-IRT). This *Review Team* was established in 2006 to provide expert review advice to sponsors, and to help assess whether there is any relation between drug concentrations and change in QT interval. FDA's *Manual of Policies and Procedures* (174) states that the *Review Team* may be available for consulting about serious ventricular arrhythmias, and that the *Review Team* will meet with a sponsor about specific product development issues only if requested to do so by a review division. FDA's review division prepares statements of development or regulatory questions to be answered by the *Review Team*.

This concerns an FDA-submission for *ivacaftor*, a drug for treating cystic fibrosis. The FDA-submission was evaluated by the QT-IRT (175). The evaluation was published on FDA's website at Jan. 2012, for NDA 202188. The *Review Team* decided that the highest dose used with human volunteers resulted in QT interval changes that were well within the safe limit. The *Review Team* wrote:

> QT-IRT recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division. The effect of multiple doses of **ivacaftor** 150 mg and 450 mg twice daily on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) ... QT study in 72 healthy subjects. In a study with demonstrated ability to detect small effects, the ... QTc ... was below 10 ms, the threshold for regulatory concern. The dose of 450 mg twice daily ivacaftor is adequate to represent the high exposure clinical scenario.

A separate document, the *Medical Review*, referred to two different safety studies, the first involving increasing doses of the study drug, and the second involving multiple doses of a constant amount of study drug. Please note that the *Medical Review* refers to the use of Fridericia's formula, not to Bazett's formula. The *Medical Review*, concluded that the study drug (ivacaftor; VX-770) did not show any significant toxicities:

> A thorough QT study was conducted for this program, and reviewed by the QT study interdisciplinary review team. The study consisted of 2 parts: **Part A** in which 8 subjects were enrolled to evaluate the safety and tolerability of increasing doses of VX-770 up to 450 mg every 12 hours (q12h), followed by **Part B** to determine if therapeutic or supratherapeutic systemic exposure to **multiple doses** of VX-770 up to 450 mg q12h prolongs the mean Fridericia-corrected QT (QTcF) interval by more than 5 milliseconds. No significant toxicities were identified in **Part A**.

[173]Package insert for ERY-TAB (Erythromycin delayed-release tablets, USP) Enteric-coated. Arbor Pharmaceuticals, LLC; July 2013.

[174]Manual of Policies and Procedures. Center for Drug Evaluation and Research. Interdisciplinary review team for QT studies; February 3, 2012 (10 pp.).

[175]Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review.