QRS Prolongation Synergy Possibilities

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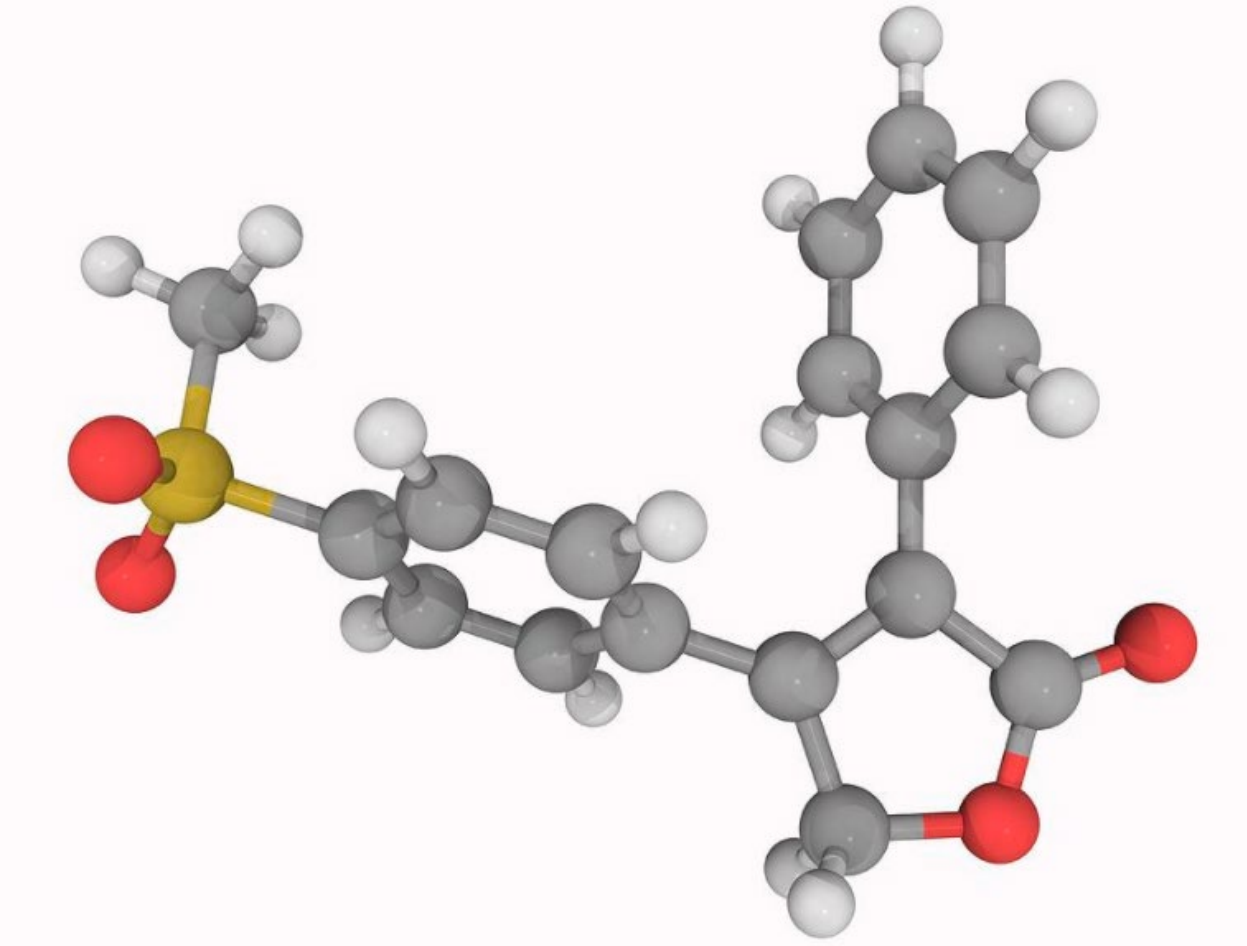
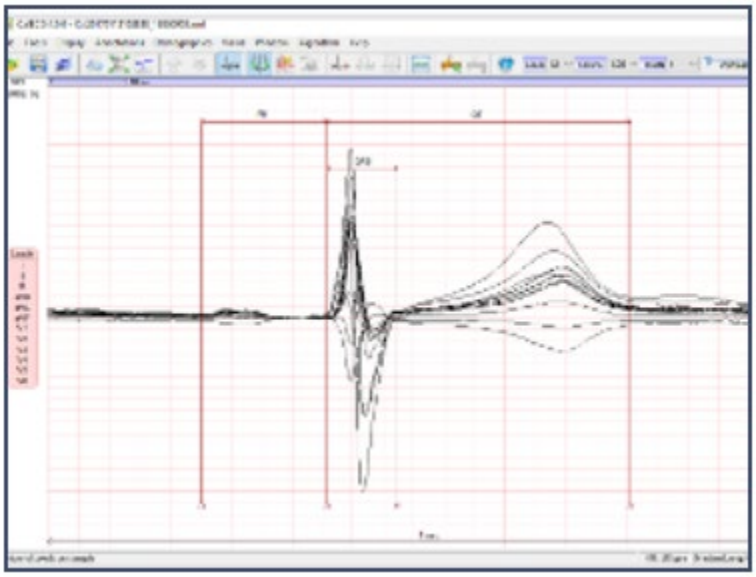
Cardiac Safety or “thorough QT” or TQT testing for QRS prolongation during drug discovery

Medidata: AMPS LLC technology allows you to add a cardiac safety front-end to your existing cloud database.

- When a drug is being designed that might have cardiac effects, a cardiac-safety, or “thorough QT study” is undergone to make sure that the drug will not cause QRS prolongation, as was the case back in 1974 with the drug Vioxx that ended up causing the deaths of thousands of people[1].
- Since then the FDA has instituted the “e14 Guidelines[2] to create a protocol for analyzing 12 lead ECGs in a CRO setting. Today, Medidata subcontracts their cardiac safety studies to companies such as IQVIA that have intellectual property on the data collection side.
- Cardiac safety investigation relates to the blockade of the human Ether-à-go-go related gene (hERG[3]) potassium channel, resulting in QRS prolongation[4] and/or (worst-case) Torsades de Pointes[5].
- hERG-altering small molecules can be flagged during drug discovery phase [ONELAB]6. By identifying molecular combinations of drugs that can affect QRS duration , one can anticipate the severity of the interaction [7].
- Long QT clinical research requires an ECG management system capable of editing aECG files to the FDA ECG Warehouse[8.] AMPS LLC[9] provides such a “front-end” for a SQL database to turn your cloud into an ECG management system.
- Thanks to the work done at Mortara, the FDA can received aECG files directly via digital transfer to the “ECG Warehouse”[10] (now called the FDA Electronic Submission Gateway).



Rofecoxib molecule



Cardiac Safety Update*: some time ago I wrote a couple community articles in the LS community regarding QRS prolongation and some updates to the market insights. Recently I've been privy to an RFP where this is extremely relevant., so I thought I would update. For some background – I was the PM at Mortara where we invented the annotated ECG format for TQT CROs as well as the 12 lead ECG Dicom protocol.*

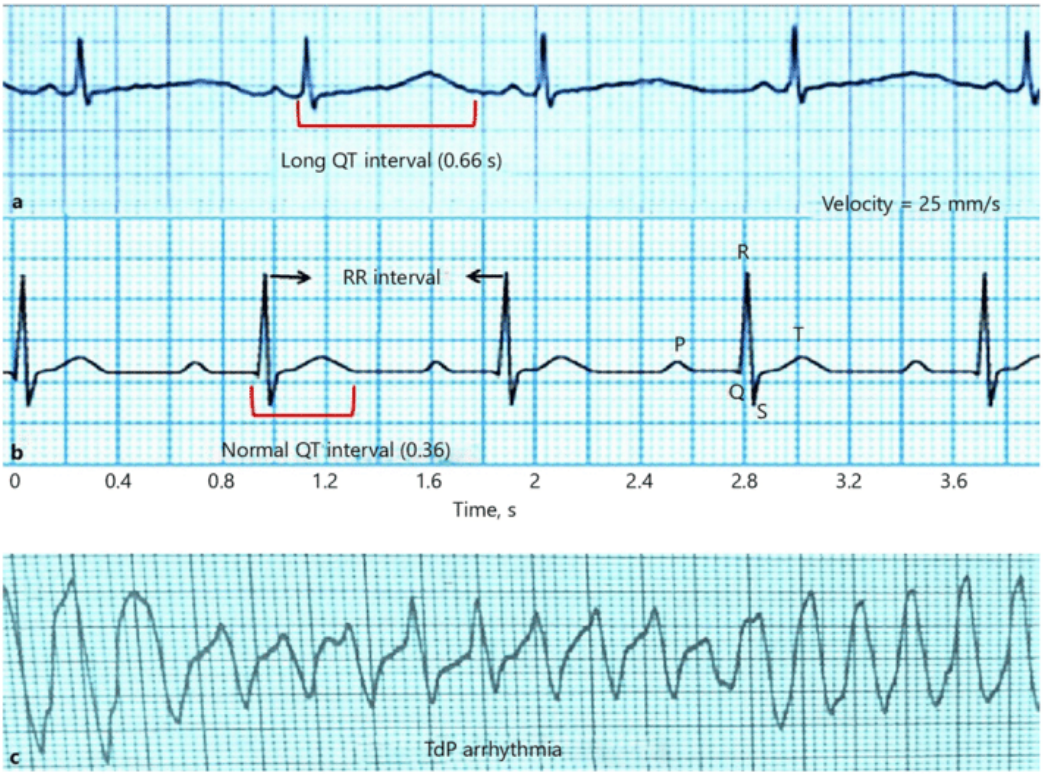
Cardiac Safety or Thorough QT, or QRS Prolongation is all about examining the origins of drugs that make the human cardiac cycle slow w-a-y down to the point of physiologically reverting to a deadly ventricular rhythm, Torsades de Pointes specifically. But QRS prolongation in and of itself is problematic as we have seen in the news recently with QRS prolongation being the specific negative cardiology attribute that Covid-19 affects.

When a drug is being designed that might have cardiac effects, a cardiac-safety, or "thorough QT study" is required to make sure that the drug will not cause QRS prolongation, as was the case back in 1999 after the drug Vioxx (rofecoxib) was released after eight clinical trials, and ended up causing the deaths of thousands of people before being voluntarily removed from the market by Merck/Monsanto[1]

Since then the FDA has instituted the "e14 Guidelines[2] to create a protocol for analyzing 12 lead ECGs in a clinical research setting in order to gauge pharmacologic effects on QRS prolongation. Typically, these "thorough QT studies" are carried out by specialized clinical research companies (CROs) such as IQVIA.

QRS prolongation etiology

Cardiac safety investigation relates to the study of the interaction of the drug blockade of the human Ether-à-go-go related gene (**hERG**[3]) potassium channel, resulting in QRS prolongation[4] and (worst-case, fatal ventricular waveform) Torsades de Pointes[5].



Cardiac Safety Ecosystem:

12 lead ECG collection device: an electrocardiograph, either stand-alone or wearable similar to Spaulding Medical's 12 lead ECG recorder, or similar. The device must be capable of meeting the basic requirements for clinical electrocardiography[7]. These requirements include minimum sampling rate, common-mode noise rejection and pass-band filter characteristics as well as basic ISO13485 and IEC 60601-2 standard for medical devices.

The device must be capable of storing the "annotated" ECG in the industry-standard annotated ECG or "aECG" file[8]. Similar to a standard XML ECG storage except has metadata for P wave onset/offset, T wave onset/offset and many other measurements not found in a diagnostic 12-lead ECG.

The ECG is sent to an ECG management system that is capable of displaying and editing annotated ECG files. **New software from AMPS LLC**[9] makes a front-end that you can add to your cloud to create an aECG-capable ECG management system that can store both 12 lead and continuous ECG recordings, as well as transfer to the **FDA Electronic Submissions Gateway or ESG**.

The main workflow difference between clinical ECG over-reading and TQT over-reading is the addition of double-blinded dual cardiologist over-readers who are primarily overseeing of the correct placement of the P Wave onset and offset for which all other measurements will be made. This data is then stored in the "annotated ECG" or aECG format, and can be directly transmitted to the FDA's "Electronic Submissions Gateway" or ESG. Alternatively, this ECG management platform is fifty per-cent the way towards a waveform-capable, cloud-based storage and reporting environment like the popular GE MUSE.

Continuous cardiology data storage: Specific to this RFP is referring to "continuous" ECG data which can be either (usually) ambulatory 24/48/72 hour Holter recordings, or long-term continuous waveform storage such as the Excel Medical (now Hillrom) "Bedmaster" data which is what the output of a GE Carescape ofRandyMilo2020(Philips Piic iX system. This is a continuous XML stream that is the industry standard (but needs to be replaced) where you can store waveforms in a signed-integer format, and along with parameter data makes up a patient monitoring stream. There are those in the CRO world who require multiples days of patient stay including all parameter data from diagnostic and/or investigative devices.

The storage protocol is very important as some vendors such as GE store this data in compressed data files that required a binary file to read. In order to have a complete gateway

The Opportunity

"The cardiac safety services market is expected to grow from USD 442 million in 2019 to reach USD 752 million by 2024, at a CAGR of 11.2%. Market growth is largely driven by factors such as the growing R&D expenditure in the pharmaceutical & biopharmaceutical industry, increased outsourcing of R&D activities, and the increasing number of clinical trials[1]."

Biovia OneLab could perform molecular searches to screen for hERG-reactive combinations (link)

References:

1. Timeline: The Rise and Fall of Vioxx: NPR (link)
2. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (link)
3. hERG (the human Ether-à-go-go-Related Gene) is a gene (KCNH2) that codes for a protein known as Kv11.1, the alpha subunit of a potassium ion channel. This ion channel (sometimes simply denoted as 'hERG') is best known for its contribution to the electrical activity of the heart: the hERG channel mediates the repolarizing IKr current in the cardiac action potential, which helps coordinate the heart's beating. (link)
4. QRS Prolongation definition: Drug-induced QRS prolongation: Wikipedia (link)

5. Cardiac safety services market: https://www.marketsandmarkets.com/Market-Reports/cardiac-safety-services-market-174488627.html
6. Electronic transmission of TQT ECG to the FDA via Electronic Submission Gateway. (link)
7. Recommendations for the Standardization and Interpretation of the Electrocardiogram (link)
8. hERG liability classification models using machine learning techniques (link)
9. HL7 annotated ECG (aECG) storage /transmission protocol (link)
10. AMPS-LLC http://www.amps-llc.com/
11. *QRS Prolongation, Thorough QT (TQT) Drug Trial Question: Why can't you include hERG ion channel assessment via molecular investigation or simulation automatically in investigational new drug (IND) submission* ? 3DS community (link)
12. *Machine learning in drug development*: Characterizing the effect of 30 drugs on the QT interval using Gaussian process regression, sensitivity analysis, and uncertainty quantification (link)
13.