

## QT IRT Reference Document

The QT Interdisciplinary Review Team (QT IRT) includes clinical, statistical, pharmacology, and clinical pharmacology reviewers, and project and database management.

The QT IRT is responsible for reviewing all thorough QT (TQT) protocols and completed QT studies, as well as protocols and results of studies intended to serve as alternatives to the TQT study. We are also available to respond to other QT-related questions.

**I** - In order for the QT IRT to review a **Thorough QT Protocol** and to accelerate the review process, the following items should be submitted:

- Electronic or hard copy of the study protocol
- Electronic or hard copy of the Investigator Brochure
- Statistical Analysis Plan
- A completed Highlights of Clinical Pharmacology Table (Table 1 shown below) – to be provided by sponsor.

**II** - In order for the QT IRT to review a **Thorough QT Study Report**, and to accelerate the review process, the following items should be submitted:

- Electronic copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- Copies of the study reports for any other clinical QT study for this product that has been performed
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- Please make sure that the ECG raw data set includes at least the followings: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, intervals (QT, RR, PR, QRS), HR, QTc [all corrected QT as end points, e.g. QTcF, QTcI (including individual correction factor), QTcB, or QTcN], Lead, ECG ID (link to waveform files if applicable).
- SAS code for the primary statistical analysis
- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- Narrative summaries and case report forms for any of the following that occur in this thorough QT study:
  - i. Deaths
  - ii. Serious adverse events
  - iii. Episodes of ventricular tachycardia or fibrillation
  - iv. Episodes of syncope
  - v. Episodes of seizure
  - vi. Adverse events resulting in the subject discontinuing from the study.
- Submission of the related ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
- A completed Highlights of Clinical Pharmacology Table (Table 1, shown below)

Note: please submit all data sets in CDISC SDTM format if possible.

**Table 1. Highlights of Clinical Pharmacology**

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

If the application is submitted electronically to the EDR, please provide the direct links to the above mentioned materials.

Also, please note that QT IRT goal is to provide a written response to consultation requests on:

- TQT or alternative study [protocols](#) (usually within [14 days](#) of receipt of the complete information)
- TQT or alternative study [reports](#) (usually within [45 days](#) of receipt of the complete information)

**QT Interdisciplinary Review Team (QT IRT)**