
POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Interdisciplinary Review Team for QT Studies

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PURPOSE

- This MAPP establishes an interdisciplinary review team (IRT) for the review of Thorough QT (TQT) protocols and studies within the Center for Drug Evaluation and Research (CDER).

BACKGROUND

- As described in the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, most new drugs should be evaluated for effects on cardiac repolarization. Prolongation of the heart-rate-corrected QT interval (QTc) on the surface electrocardiogram (ECG) indicates an effect on cardiac repolarization and may predict risk for sometimes-fatal ventricular arrhythmias, chiefly torsades de pointes. The results of these studies may affect regulatory decisions about risk-benefit and/or the need for a risk management program for a product.
- ICH E14 suggests that mean effects smaller than 5 ms (determined by ruling out an effect as large as 10 ms at the one-sided upper 95 percent confidence limit) are not associated with levels of risk “of regulatory concern.” Therefore, drugs with mean effects on the QTc smaller than 5 ms at therapeutic doses in a well-designed and carefully conducted TQT study generally do not require extensive evaluation

of QT effects in phase 3 studies. Exclusion of such a small effect on QTc requires careful attention to study design, conduct, and analysis. Although ICH E14 outlines some of the basic principles of a TQT study, additional nuances are becoming apparent as industry, academics, and the Food and Drug Administration (FDA) gain experience with these studies.

- Therefore, CDER established an IRT to provide expert review advice to sponsors and review divisions on TQT studies and to contribute to the evolution of the science by developing alternative methods for evaluating repolarization effects.

POLICY

- CDER has established an IRT for the evaluation of TQT and alternative study protocols and the results of such studies.
- The IRT is comprised of:
 - Medical officers from the Division of Cardiovascular and Renal Products (DCRP).
 - Cardiovascular pharmacologists/toxicologists from the DCRP.
 - Regulatory project managers (RPMs) from the DCRP.
 - Data managers from the DCRP.
 - Clinical pharmacologists from the Office of Clinical Pharmacology.
 - Statisticians from the Office of Biostatistics.
- Team members will remain associated with their original office for administrative issues such as supervision, travel, and awards. The DCRP will manage the IRT's day-to-day operations.
- Review divisions will consult the IRT on all TQT study protocols and results, as well as on protocols and results of studies intended to serve as alternatives to the TQT study (e.g., exposure-response studies).
- Review divisions and offices of drug evaluation will remain responsible for any regulatory decisions pertaining to their drug products. These decisions include matters relating to advice to sponsors on study design, the final interpretation of study results, approval decisions, and labeling.

- The IRT will be available for consultation on other matters relating to serious ventricular arrhythmias, but any such consultation is voluntary on the part of the review divisions. The IRT is not intended to serve as consultant for other electrocardiographic concerns or other cardiovascular safety concerns; those issues should be directed to DCRP.
 - The IRT will meet with a sponsor about specific product development issues only if requested to do so by a review division. It is up to the review divisions to decide whether to mediate any communications between the IRT and sponsors to obtain information necessary for the IRT to complete a consultative review.
 - Other CDER offices and other centers within the FDA may consult the IRT about QT protocols and study reports.
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RESPONSIBILITIES

Review divisions **must** do the following:

- Provide timely notification (usually within 2 weeks of receipt by the review division) of a new TQT or alternative study protocol to the IRT.
- Provide timely notification (usually within 2 weeks of receipt by the review division) of a new TQT or alternative (exposure-response or other study intended to be the principal assessment of repolarization effects) study report to the IRT.
- Prepare succinct statements of development or regulatory questions to be answered by the IRT and submit the data as specified in the QT IRT Reference Document (see Attachment 1).
- Have the RPM disseminate the recommendations of the IRT to the assigned reviewers before providing the comments to the sponsor.
- Have the RPM provide the IRT with a copy (usually by electronic cc) of all communications to the sponsor related to QT issues.

Review divisions **may** seek consultation from the IRT on the following:

- Preclinical assessment of drug effects on cardiac repolarization.
- When to do a TQT study during a development program.

- Phase 2 and phase 3 evaluations, such as pharmacokinetic and pharmacodynamic evaluations relating drug exposure to QTc, outlier analyses, or analyses based on Holter recordings.
- Interpretation of safety events possibly related to ventricular cardiac arrhythmias.
- Risk management programs for serious ventricular arrhythmias.
- Labeling.
- Protocols for QT-related studies revised according to comments provided by the IRT if the review division is unsure as to whether the sponsor's response is adequate. If the review division requests consultation, the consult request should identify the items the division finds unclear.

The IRT must do the following:

- Provide a written response to consultation requests on:
 - TQT or alternative study protocols (goal is within 14 days of receipt of the complete information).
 - TQT or alternative study reports (goal is within 45 days of receipt of the complete information).
 - Other clinical trial issues pertaining to the assessment of the serious ventricular arrhythmias potential of drugs.
- Participate in meetings with the review division, if requested.
- Establish and maintain an administrative tracking system for TQT and alternative studies.
- Establish and maintain an integrated database of TQT and alternative study results, including demographics, ECG interval measurements, study drug-related interventions, and drug concentrations in plasma.
- Monitor the ECG warehouse (www.ecgwarehouse.com) and maintain the linkage between the clinical database and the ECG warehouse. The Study Data Tabulation Model dataset format has a place to link the ECG findings to specific ECGs. The IRT data manager will establish (on the basis of subject identifier, date, and time) the linkage for submissions in other formats.

- Develop and maintain a practical guide to the design of TQT studies. Initially, this will be an internal document continuously updated with lessons learned by the IRT. In time, it could evolve into formal guidance for industry.
- Develop and maintain a practical guide to the review of TQT studies. Initially, this will be an internal document continuously updated with lessons learned by the IRT. In time, it could evolve into a MAPP.
- Advise, monitor, and technically or collaboratively support intramural and extramural research involving the data from TQT studies.
- Communicate activity and lessons learned inside and outside the FDA.
- Maintain an intranet Web site or eRoom for the persistent artifacts of its activities — databases, consultative reviews, best practices, and review tools.

The IRT may do the following:

- Require Office of Scientific Investigations inspections for a study it has been asked to review.

Specific IRT members will do the following:

- The DCRP Division Director will select a reviewer to assume responsibility for the overall scientific leadership of the IRT reviews.
- The DCRP data manager will set up and maintain the databases used by the IRT.

The CDER QT Working Group will do the following:

- Act as an advisory panel for the IRT.

PROCEDURES

- Consult requests to the IRT should be submitted to the DCRP according to the QT IRT Reference Document (see Attachment 1).
- Consult requests must specify questions that the review division would like addressed by the IRT.
- The most current Investigator Brochure for the product being studied should be submitted with the consult request.

- Where such information is available, consultation requests should be accompanied by a summary of information on preclinical assessment of cardiac safety, in vitro and in vivo effects on ion channels, preclinical and clinical pharmacokinetics, the dose range being studied for effectiveness, the intended patient population, and clinical safety. The locations for any relevant complete reports in the submission also should be provided. If other members of the pharmacologic class have had QT problems, these should be described briefly.
 - Consult requests to the IRT must specify the time constraints for a response by the IRT. If the proposed timing is problematic, the IRT RPM will contact the consulting review division to negotiate the timing.
 - The IRT will jointly author consult reviews, with each review team member contributing sections relevant to his or her area of expertise. Joint authorship does not necessarily result in all contributing parties signing the review in the electronic document system. Although the IRT should meet to discuss issues arising in its reviews, there is no particular expectation regarding consensus. Disagreements on the interpretation of the data or advice will be represented fairly in the final document. The IRT scientific leader will assign a lead author to each review to ensure an overall consistent style and to minimize redundancy. As with other consultative reviews from the DCRP, the DCRP Division Director or designee will provide final sign-off. When the review team cannot reach consensus, a statement of the division's best advice will accompany the sign-off.
 - At its discretion, the CDER QT Working Group may periodically review the work products of the IRT. The CDER QT Working Group may offer advice on procedural or scientific matters.
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REFERENCES

1. ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.¹
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DEFINITIONS

- **CDER QT Working Group** — A group formed to study the issue of QT/QTc prolongation and torsades de pointes as an adverse reaction resulting from QTc prolongation in humans. The mission of the working group is to provide recommendations for a consistent, standardized approach to the conduct and

¹ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

review of preclinical and clinical studies of the effect of drugs on the QT interval. This group provides general advice and does not review data from specific development programs.

- **Thorough QT (TQT) Study** — A study that is “intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization” (ICH E14). The study may involve single or multiple doses, enroll healthy volunteers or patients, and be of parallel or crossover design. There usually is a positive control agent, the intent of which is to ensure that the study has adequate assay sensitivity.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT 1: 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.

1. 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 (see Table 1)

2. 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 Brochure
 - Annotated case report form
 - Copies of the study reports for any other clinical QT study for this product that has been performed
 - A Define file that describes the contents of the electronic datasets
 - Electronic datasets as SAS transport files
 - The ECG raw dataset that includes at least the following: 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 endpoints, 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
 - Dataset 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:
 - Deaths
 - Serious adverse events
 - Episodes of ventricular tachycardia or fibrillation
 - Episodes of syncope
 - Episodes of seizure
 - Adverse events resulting in the subject discontinuing from the study
- Submission of the related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table (see Table 1)

Note: Please submit all datasets 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) C_{max} and AUC
	Multiple Dose	Mean (%CV) C_{max} 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)
	T_{max}	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal $t_{1/2}$	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)

continued

Table 1, continued

Intrinsic factors	Age	Specify mean changes in C_{max} and AUC
	Sex	Specify mean changes in C_{max} and AUC
	Race	Specify mean changes in C_{max} and AUC
	Hepatic and Renal Impairment	Specify mean changes in C_{max} and AUC
Extrinsic factors	Drug Interactions	Include listing of studied DDI studies with mean changes in C_{max} and AUC
	Food Effects	Specify mean changes in C_{max} 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 C_{max} 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 the QT IRT's 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)