POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Interdisciplinary Review Team for Cardiac Safety Studies

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PURPOSE

- This MAPP establishes a cardiac safety interdisciplinary review team (CS IRT) for the review of protocols and study reports to assess (1) proarrhythmic risk based on clinical electrocardiogram (ECG) data and nonclinical data as well as (2) blood pressure elevation risk of medicinal products within the Center for Drug Evaluation and Research (CDER).

BACKGROUND

- Most new drugs are evaluated for effects on cardiac repolarization. Prolongation of the heart-rate-corrected QT interval (QTc) on the surface ECG indicates an effect on cardiac repolarization and may predict risk for sometimes-fatal ventricular arrhythmias, chiefly torsade de pointes. The current cardiac safety testing paradigm for preventing drugs from being approved with an unanticipated risk of torsade de pointes is performed according to two Food and Drug Administration (FDA) guidances, *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005) and *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005), that recommend evaluating a drug's direct effects on cardiac human ether-a-go-go-related-gene (hERG) potassium channels and QTc interval captured on ECG, respectively. The results of these studies may affect regulatory

decisions about benefit-risk or the need for a risk management program for a product.

- The centerpiece of FDA's E14 guidance is the thorough QT (TQT) study, designed to detect mean effects smaller than 5 milliseconds (ms) (determined by ruling out an effect as large as 10 ms at the one-sided upper 95 percent confidence limit). Drug products with mean effects on the QTc smaller than 5 ms at therapeutic exposures 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.

- Concentration-QTc modeling with high quality ECG measurements in placebo-controlled studies without a positive control (e.g., single ascending dose (SAD) and multiple ascending dose (MAD) studies) can be used as a substitute for a TQT study as described in Guidance for Industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers* (June 2017) (E14 Q&A Q12), provided that the exposure coverage is sufficiently high to waive the need for a separate positive control.[1] If a TQT study or substitute for a TQT study is not feasible, the potential for QTc prolongation can be evaluated in an alternative QT study (E14 Q&A Q13). In the absence of placebo and a positive control there is a reluctance to conclude absence of an effect similar to a TQT study or a substitute for a TQT study; however, if the one-sided upper 95 percent confidence limit is less than 10 ms, then it is unlikely that the effect is as large as 20 ms.

- Integrated nonclinical data from *in vitro* assays (e.g., cardiac ion channel assays) and *in vivo* ECG studies in animals can be used to support the interpretation of clinical ECG findings per the Guidance for Industry *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers* (August 2022) (E14 and S7B Q&A Q17).[2] Depending on the findings of the clinical (and if included, integrated nonclinical) data additional follow-up assays could also be appropriate. This could include isolated preparations (e.g., *in vitro* human cardiomyocytes – E14 and S7B Q&A Q20 – Q23) or proarrhythmia models (e.g., *in silico* – E14 and S7B Q&A Q29).[3]

- Another important cardiac safety issue is a drug's ability to increase blood pressure. Elevated blood pressure is known to increase the risk of stroke, heart attack, and death. The effect of a drug on blood pressure can be an important

[1] E14 Q&A Q12 and Q13 correspond to questions 5.1 and 6.1 in the ICH E14: *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Questions & Answers (R3)* (ICH E14 Q&A), respectively.
[2] E14 and S7B Q&A Q17, Q20 – Q23, and Q29 correspond to questions 1.1, 2.2 - 2.5, and 4.1 in the ICH E14/S7B: *Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential, Questions & Answers* (ICH E14/S7B Q&A), respectively.
[3] Ibid

consideration in the benefit-risk assessment. Epidemiologic studies show that risk of stroke, heart attack, and death is related to blood pressure as a continuous function, and that sustained increases in blood pressure correlate with long-term increased risk of cardiovascular adverse events. Even small, sustained increases in blood pressure (2 to 3 millimeters of mercury (mmHg)) chronically would be expected to have such an effect. The Ambulatory Blood Pressure Monitoring (ABPM) study is capable of detecting small changes in blood pressure. Detection of such small increases in blood pressure requires careful attention to study design, conduct, and analysis. Although the draft guidance *Assessment of Pressor Effects of Drugs* (February 2022) outlines some of the basic principles of an ABPM study, it is anticipated that additional nuances will become apparent as industry, academics, and FDA gain experience with these studies.

- CDER established the Interdisciplinary Review Team (IRT) for QT studies in 2006 to provide expert and consistent review advice to sponsors, applicants, and OND Clinical review divisions on TQT studies. This approach will now consider an integrated assessment of the nonclinical assays to elucidate the proarrhythmic risk of drugs. Furthermore, CDER has now expanded the scope of the CS IRT to provide expert and consistent review advice on ABPM studies and to contribute to the evolution of the science by developing study designs and methods for evaluating blood pressure effects and the risk of cardiac adverse events.

POLICY

- CDER established a CS IRT for the evaluation of:
  - QT study protocols and results of such studies (i.e., TQT study, substitute for a TQT study, or alternative QT study).
  - ECG parameters measured in clinical studies to support proarrhythmic assessment (e.g., clinical studies with intensive ECG monitoring and/or monitoring for serious ventricular arrhythmias).
  - ABPM study protocols and results of such studies.
- The CS IRT is comprised of:
  - Medical officers, clinical analysts, and other clinical scientists from the Division of Cardiology and Nephrology (DCN).
  - Cardiovascular pharmacologists/toxicologists from the Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN).
  - Regulatory project manager (RPM) from DCN (CS IRT RPM).

  - Data managers from DCN.

  - Clinical pharmacologists from the Office of Clinical Pharmacology (OCP).

  - Statisticians from the Office of Biostatistics (OB).

- Team members remain associated with their original office for administrative issues such as supervision, travel, and awards. DCN will manage the CS IRT's day-to-day operations. The DCN Division Director or the designated supervisor may select a lead reviewer to assume responsibility for the overall scientific content of the IRT reviews.

- OND Clinical review divisions are expected to contact the CS IRT on all:

  - Study protocols and results of QT studies (i.e., TQT studies, substitute for TQT studies, or alternative QT assessments).

  - Requests for confirmation that a QT assessment (i.e., TQT study, substitute for a TQT study, or alternative QT study) is not necessary.

  - Nonclinical integrated QTc/proarrhythmic risk assessments, including study protocols and results for cardiac ion channel inhibition assays and *in vivo* ECG studies in animals; proarrhythmia models (e.g., *in silico* proarrhythmia models); and proarrhythmic effects measured in isolated cardiac preparations.

  - ABPM study protocols and results.

- The CS IRT is available for advice on other matters (not listed above) relating to serious ventricular arrhythmias, but requesting such advice is up to the discretion of the OND Clinical review divisions.

- OND Clinical review divisions and Offices 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 CS IRT meets with sponsors about specific product development issues only if requested to do so by an OND Clinical review division. It is the OND Clinical review divisions that mediate communications between the CS IRT and sponsors to obtain information necessary for the CS IRT to complete a consultative review.

- Other CDER offices and other centers within the FDA may contact the CS IRT about QT- or ABPM-related protocols and study reports.

RESPONSIBILITIES

OND Clinical review divisions:

- Provide timely notification to the CS IRT (usually within 2 weeks of receipt by the review division) that includes:
  - a meeting background package with questions related to the proarrhythmic risk assessment (clinical or integrated nonclinical assessments) or ABPM study assessment
  - requests for confirmation that a QT assessment is not necessary
  - a new TQT, substitute for a TQT, or alternative QT study protocol and subsequent revised versions
  - a new TQT, substitute for a TQT, or alternative QT study report
  - a new ABPM study protocol and subsequent revised versions
  - a new ABPM study report
- Prepare succinct statements of development or regulatory questions to be answered by the CS IRT and submit the referenced data.

OND Office of Regulatory Operations (ORO) Project Management Staff:

- Submit the request for advice from CS IRT on behalf of the OND Clinical review division.
- Disseminate the recommendations of the CS IRT to the assigned reviewers for consideration before taking any further actions.
- Provide the CS IRT with a copy (usually by email) of all communications to the sponsor related to QT or ABPM issues.

OND Clinical review divisions may seek advice from the CS IRT on:

- The need and timing of a QT assessment or an ABPM study in the clinical development program.

- Labeling for drugs with QTc prolongation or with effects on PR or QRS intervals or with BP elevations based on ABPM study results.

- Nonclinical assessments of drug effects on cardiac repolarization as described in guidance *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005).

- Interpretation of safety events possibly related to ventricular arrhythmias.

- Risk management programs for substantial QTc prolongation or serious ventricular arrhythmias.

- Protocols for QT-related studies revised according to comments provided by the CS IRT (e.g., if the OND Clinical review division is unsure whether the sponsor's response is adequate). If the OND Clinical review division requests advice, then the request should identify the items the division finds unclear.

The CS IRT:

- Provide a written response to requests for advice on:

  – Questions related to the proarrhythmic risk assessment in a briefing document for industry meetings (goal is within 14 calendar days of receipt of complete information).

  – TQT, substitute for TQT, or alternative QT study protocols (goal is within 14 calendar days of receipt of the complete information).

  – TQT, substitute for TQT, or alternative QT study reports (goal is within 45 calendar days of receipt of the complete information).

  – Questions related to the evaluation of blood pressure effects in a briefing document for industry meetings (goal is within 14 calendar days of receipt of complete information).

  – ABPM study protocols (goal is within 14 calendar days of receipt of the complete information).

  – ABPM study reports (goal is within 45 calendar days of receipt of the complete information).

  – Other clinical trial issues pertaining to the assessment of the proarrhythmic or pressor effect potential of drugs.

- Participate in meetings with the OND Clinical review division, if requested.

- Establish and maintain an administrative tracking system for ongoing and completed reviews.

- Develop and maintain technical specifications documents that provide detailed information and specifications for the content of data sets that should be submitted as part of the sponsor's or applicant's QT studies, ABPM studies, and nonclinical QT assessment (e.g., cardiac ion channel inhibition assay results or *in vivo* ECG studies).

- Establish and maintain a database of study results (e.g., ECG interval measurements, ABPM measurements, study drug-related interventions, and drug concentrations in plasma).

- Establish and maintain a process for reviewing ECG waveforms to support the review of QT assessments.

- Establish and maintain a database of nonclinical study results (e.g., cardiac ion channel inhibition assay studies, *in silico* reconstruction of the action potential duration, ECG intervals or arrhythmias; and ionic currents measured in isolated human cardiac myocytes).

- Develop and maintain templated internal practical review guides for QT and ABPM, that will be continuously updated with lessons learned by the CS IRT.

- Advise, monitor, and technically or collaboratively support intramural and extramural research involving the data from electrophysiological, QT and ABPM studies.

- Communicate cardiac safety-related activity and lessons learned inside and outside FDA.

- Utilize appropriate tools for internal storage, sharing of reviews, best practices, and review tools.

The CS IRT may:

- Request expert review from disciplines that are not permanent members of the CS IRT.

- Request Office of Scientific Investigations (OSI) issue inspections for a

study it has been asked to review.

PROCEDURES

- QT related requests for advice from the CS IRT should be submitted using the approved CDER Electronic Record Keeping System (ERKS), ensuring that the advice request is clearly marked as "QT advice".

- ABPM-related requests for advice from the CS IRT should be submitted using the ERKS, ensuring that the advice request is clearly marked as "ABPM advice".

- Requests for advice should specify questions that the OND Clinical review division would like addressed by the CS IRT.

- The locations for all relevant review information (e.g., meeting packages, study reports, protocols, previous regulatory communications, Investigator Brochure) should be provided in the request for advice.

- Advice requests should specify the time constraints for a response by the CS IRT. If the proposed timing is problematic, the CS IRT RPM will contact the OND Clinical review division requesting the advice to negotiate the timing.

- The CS IRT jointly authors reviews, with other team members contributing sections relevant to their area of expertise. Joint authorship does not necessarily result in all contributing parties signing the final review. Although the CS IRT should meet to discuss issues arising in its reviews, there is no expectation regarding consensus, but the CS IRT strives to achieve alignment. Disagreements on the interpretation of the data or advice should be fairly represented in the final document. When the CS IRT cannot reach consensus, a statement of the DCN's best advice by the DCN Division Director or designated supervisor will be included in the final review.

- The DCN Division Director or designated supervisor provides final clearance.

REFERENCES

- Draft Guidance for Industry: *QTc Information in Human Prescription Drug and Biological Product Labeling* (August 2023).

- Guidance for Industry: *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers* (August 2022).

- Draft Guidance for Industry: *Assessment of Pressor Effects of Drugs* (February 2022).

- Guidance for Industry: *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers* (June 2017).

- Guidance for Industry: *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005).

- Guidance for Industry: *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005).

- ICH E14/S7B Guideline: *Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential, Questions and Answers* (21 February 2022).

- ICH E14 Guideline: *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Questions & Answers (R3)*, (10 December 2015).

- Interdisciplinary Review Team for Cardiac Safety Studies web page (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt)

DEFINITIONS

- **Alternative QT Study** – An alternative QT study can be appropriate if a TQT study or a substitute for a TQT study is not possible. This situation can arise under any of the following scenarios: a placebo-controlled comparison is not possible; safety considerations preclude administering supratherapeutic doses to obtain high clinical exposures and/or safety or tolerability prohibit the use of the product in healthy participants. The alternative QT study should incorporate many of the usual TQT design features as possible.[4]

- **Ambulatory Blood Pressure Monitoring (ABPM) Study** – A clinical study designed to describe blood pressure effects over 24 hours. ABPM measurements should be performed in the patient population for which the drug is being developed, either in a targeted study or as part of a larger study already being conducted for other purposes in this population.

[4] E14 Q&A Q12 and Q13 correspond to ICH E14 Q&A 5.1 and 6.1, respectively.

- **Nonclinical integrated risk assessment** – Nonclinical strategy for assessing risk of delayed ventricular repolarization and QT interval prolongation using the *in vitro* rapidly activating delayed rectifier potassium current (I_{Kr})/hERG assay and *in vivo* QT assay as well as optional follow-up studies. These nonclinical investigations support the planning and interpretation of First-in-Human studies and can contribute to a risk assessment for QTc prolongation and arrhythmia in later stages of development when clinical data are available.

- **Substitute for a TQT Study** – A study that includes high-quality ECGs, placebo-control, and sufficient exposure coverage to support waiving the requirement for a separate positive control (E14 Q&A guidance Q12). Commonly, early phase studies such as SAD or MAD are used as substitutes for TQT studies.

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

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
10/16/2007	Initial issuance	n/a
02/03/2012	Rev. 1	Accounting of edits not available.
10/21/2024	Rev. 2	Updated to align with current OND organizational structure, applicable user fee agreements (UFA) commitments, and current CDER workflow procedures and best practices.