Recent insights from the FDA QT-IRT on concentration-QTc analysis and requirements for TQT study (*'waiver')* substitution

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Disclaimer

- The views expressed in this presentation are that of the author and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

Outline

- QT-IRT statistics
- Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)
  - Sample size
  - Exposure margin
- Common issues in submissions
- QT correction for heart rate effects
- Modeling analysis and reporting
- Forthcoming changes in data specifications

QT-IRT statistics for C-QT submissions under ICH E14 Q&A (R3)

➢ Dec 2015 - April 2018 (non-oncology products):

- TQT substitutions (No moxifloxacin)
  - 14 favorable recommendations based on submitted data
    - 9 SAD studies, 4 SAD/MAD studies, 1 Other
  - 2 not recommended
- Alternative TQT study (C-QT primary analysis- drug/moxifloxacin)
  - 1 completed study reviewed ('no effect' label)
  - 14 protocols agreeable; 3 recommended to change design; 2 recommended to change primary to central tendency analysis

- Exposure margin (covering high clinical exposures, waiving positive control) is the predominant reason for not agreeing with the TQT substitution proposals

Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)[1]

- Study Design
- ECG Quality
- Dose range
- **Sample size**
- **Assay Sensitivity**
- C-QTc analysis

[1]Refer to following publicly available slides (CSRC 2016):
http://cardiac-safety.org/wp-content/uploads/2016/12/S1_3_Marathe.pdf

General guidance for sample size

➢ Sample size for Phase 1 type C-QT assessment

- **Subjects with placebo:** Plan for at least 8-10 evaluable subjects; can be pooled from different cohorts (e.g., 6:2 randomization to Trt:Placebo across 4-5 dose cohorts)

➢ Sample size for alternative TQT (C-QT analysis for drug treatment and positive control)

- **Subjects with moxifloxacin:** Plan for at least 20-24 subjects (and equal number of placebo subjects for parallel study)[2]
- **Subjects with drug treatment:** Plan using E-R simulations with expected effect size/variability etc.

[2]Huang D. *et al*, manuscript under review in *J Pharm Stat*

General guidance for assay sensitivity

➢ Criteria for waiving requirement for positive control

- Evaluation of sufficiently high multiples (at least 2-fold) of highest clinically relevant exposure scenario*

*Highest exposure (C_{max}) at steady state due to intrinsic (e.g., organ impairment) or extrinsic factors (e.g., metabolic inhibition)

  - Based on normal dosing regimen (not the dosing regimen for sub-population); model based estimate can be acceptable

Example: A product with recommended dose of 20 mg BID in normal and 10 mg BID in severe renal impairment population.

Highest clinically relevant exposure from QT-IRT's perspective: Mean $C_{max,ss}$ with 20 mg BID (not 10 mg BID) dosing in severe renal impairment population.

General guidance for assay sensitivity

➢ Criteria for waiving requirement for positive control

- Evaluation of sufficiently high multiples (at least 2-fold) of highest clinically relevant exposure scenario*
- Non-pharmacological approaches (e.g. bias evaluation[3,4]) as an alternative to requirement for multiple fold exposure under consideration

[3]Darpo B., *CSRC-FDA workshop*, 2016

[4]Ferber G. *et al*, *JCP*, June 2016

Some common issues in submissions

- Expectation of exposure margin to waive the requirement of a positive control not achieved/unknown
  - Observed/estimated impact of organ impairment/DDI unknown
  - Not feasible to achieve requisite higher exposures (tolerability, pill-burden, saturable absorption etc.)
- Exposures for major metabolite(s) with long half-life not covered
- ECG sampling includes T_{max} of parent drug but no sampling near T_{max} of major metabolite
- In single dose trial, ECG sampling not for sufficient duration (at least 24 hours) to evaluate potential delayed effect
- Justification for pooling not adequate: e.g., Placebo absent in some studies

QT correction for heart rate effects

- The product is not likely to increase or decrease the heart rate significantly in the study
  - Use QTcF for the primary analysis
- The product is likely to increase or decrease the heart rate significantly (e.g., >10 bpm) in the study
  - Consider alternative methods[5] (e.g., QTcI), with wide enough span of heart rates at drug-free baseline visits to cover on treatment changes in heart rate within each individual
  - In cases where it may not be feasible to cover range of on-treatment large heart rate changes in off-treatment visits, consider engaging with the Agency to explore alternatives to bridge the information for adequate characterization of QTc/proarrhythmic effects

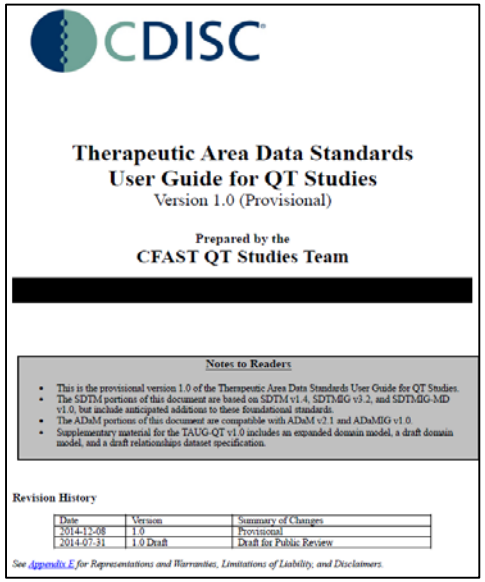
[5]Garnett C. *et al*, *Am Heart J*, 2012;163(3):912-30

Modeling analysis and reporting

- For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "*Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "*Correction to: Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).

Changes in Data Specifications

- Current state/issues: Dataset submissions in different formats (SDTM/ADaM, NONMEM, Other); Inconsistent coding of ADEG and ADPC pose challenge for C-QTc analysis datasets etc. → Difficulty for automated data quality checks, creation of standard analysis datasets etc.


CDISC

Therapeutic Area Data Standards User Guide for QT Studies
Version 1.0 (Provisional)

Prepared by the
CFAST QT Studies Team

Notes to Readers

- This is the provisional version 1.0 of the Therapeutic Area Data Standards User Guide for QT Studies.
- The SDTM portions of this document are based on SDTM v1.4, SDTMIG v3.2, and SDTMIG-MD v1.0, but include anticipated additions to these foundational standards.
- The ADaM portions of this document are compatible with ADaM v2.1 and ADaMIG v1.0.
- Supplementary material for the TAUG-QT v1.0 includes an expanded domain model, a draft domain model, and a draft relationships dataset specification.

Revision History

Date	Version	Summary of Changes
2014-12-08	1.0	Provisional
2014-07-31	1.0 Draft	Draft for Public Review

See *Appendix E for Representations and Warranties, Limitations of Liability, and Disclaimers.*

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Additional variables in ADEG to support C-QTc analysis

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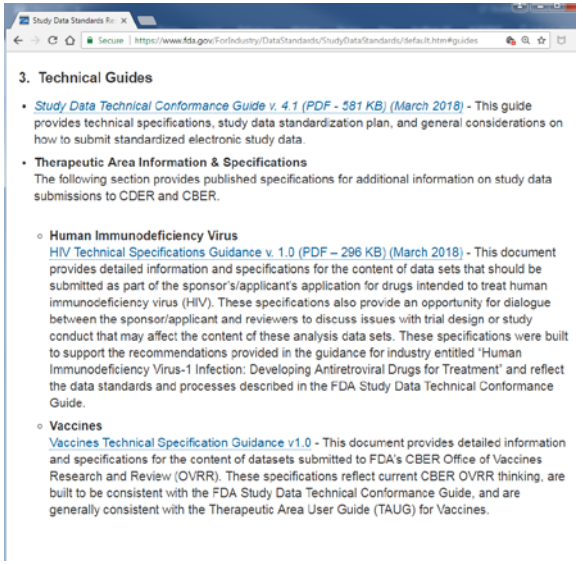
3. Technical Guides

- *Study Data Technical Conformance Guide v. 4.1 (PDF - 581 KB) (March 2018)* - This guide provides technical specifications, study data standardization plan, and general considerations on how to submit standardized electronic study data.
- **Therapeutic Area Information & Specifications**
  The following section provides published specifications for additional information on study data submissions to CDER and CBER.
  - **Human Immunodeficiency Virus**
    HIV Technical Specifications Guidance v. 1.0 (PDF – 296 KB) (March 2018) - This document provides detailed information and specifications for the content of data sets that should be submitted as part of the sponsor's/applicant's application for drugs intended to treat human immunodeficiency virus (HIV). These specifications also provide an opportunity for dialogue between the sponsor/applicant and reviewers to discuss issues with trial design or study conduct that may affect the content of these analysis data sets. These specifications were built to support the recommendations provided in the guidance for industry entitled "Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment" and reflect the data standards and processes described in the FDA Study Data Technical Conformance Guide.
  - **Vaccines**
    Vaccines Technical Specification Guidance v1.0 - This document provides detailed information and specifications for the content of datasets submitted to FDA's CBER Office of Vaccines Research and Review (OVRR). These specifications reflect current CBER OVRR thinking, are built to be consistent with the FDA Study Data Technical Conformance Guide, and are generally consistent with the Therapeutic Area User Guide (TAUG) for Vaccines.

ADEG: ECG data
ADPC: PK data
ADQT: Heart rate correction of QT

Summary

- Success in alleviating the need for TQT studies for multiple development programs based on C-QT analysis of data in early phase studies following ICH E14 Q&A (R3) implementation

- Outlined general guidance for sample size and assay sensitivity aspects

- Some challenges and potential solutions for design/analysis
  - Bias evaluation as an alternative to requirement for multiple fold exposure margin (Dr. Johannesen)
  - Handling multiple moieties in a C-QT paradigm (Dr. Ferber)
  - Handling heart rate effects (Dr. Malik)


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