Revised E14 Q&As and Presentation of Examples to Highlight the Impact of Nonclinical Data on Clinical Development and Interpretation

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History of ICH E14 Q&A

2005 E14

2008 Q&A

- ECG methodology
- Sex differences
- Positive control
- Study design

2012 Q&A (R1)

- ECG methodology
- Sex difference
- Late stage ECG monitoring

2014 Q&A (R2)

- Alternative study design (6.1)
- Combination products
- Large proteins
- Concentration-response

2015 Q&A (R3)

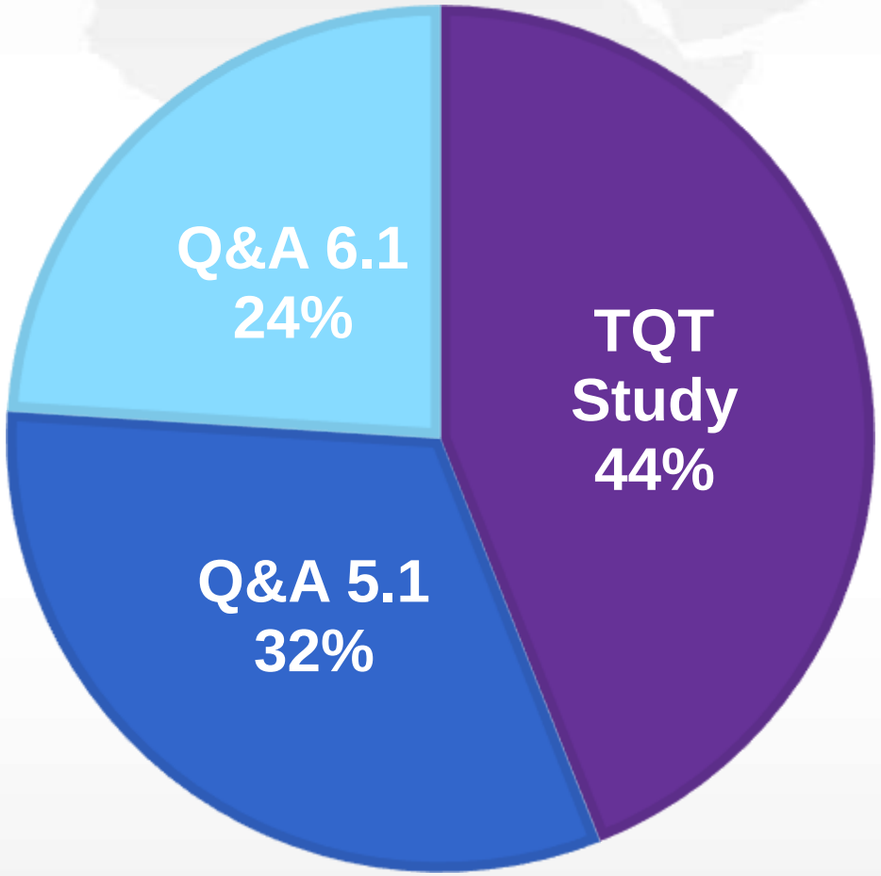
- Concentration-response analysis for regulatory decision-making (5.1)

https://database.ich.org/sites/default/files/E14_Q%26As_R3_Q%26As.pdf

Value Proposition of Revised E14 Q&As

Q&A 6.1: Strength of evidence for low QT risk in alternative studies

Q&A 5.1: Phase 1 studies that can be used to assess QTc effects



Decrease the number of thorough QT (TQT) studies

QT Study Reports (FDA, 2016–20)

Dose and Exposure Definitions

Term	Definition	Example for Drug X (assume no accumulation and linear pharmacokinetics)
Therapeutic dose	Dose evaluated in Phase 3 trial or recommended in product labeling	10 mg QD
Clinical exposure	Mean steady state maximum concentration ($C_{max,ss}$) associated with the *maximum therapeutic dose*	$C_{max,ss}$ = 100 ng/ml
High clinical exposure scenario	Increase in exposure ($C_{max,ss}$) when the *maximum therapeutic dose* is given with intrinsic or extrinsic factors	3-fold $C_{max,ss}$ with DDI Target: 300 ng/ml
Supratherapeutic dose (TQT study)	Dose that provides exposures that cover high clinical exposure scenario	Dose gives C_{max} of at least 300 ng/ml ≥30 mg
Dose/exposure needed to waive positive control in Q&A 5.1	≥2-fold the high clinical exposure	Dose gives C_{max} of at least 600 ng/ml ≥60 mg

Q&A (R3) 5.1: Use of Concentration Response Modeling of QTc Data (12/2015)

- **Substitute for a TQT study should have the following elements:**
  - Clinical studies characterizing the QT response at doses that reflect high exposure scenario
  - High-quality electrocardiogram (ECG) recording and analysis sufficient to support a valid assay for ECG intervals
  - A separate positive control is not necessary if data characterizing the response is acquired at sufficiently high multiple of the clinically relevant exposure (i.e., ≥2-fold the high exposure scenario)

Q&A (R3) 6.1: Drugs That Cannot Undergo a Conventional QT Assessment (12/2015)

- **Alternative study designs conducted in patients that do not include placebo or positive controls and do not evaluate QT response above clinical exposures**
- **Decision-making under Q&A 6.1**
  - There is reluctance to draw conclusions of lack of an effect in an absence of a positive control; however, if the upper bound of the two-sided 90% confidence interval around the estimated maximal effect on ΔQTc is less than 10 msec, the treatment is unlikely to have an actual mean effect as large as 20 msec
  - Interpretation: Drug did not cause large mean increases (i.e., 20 msec) in the QTc interval at the therapeutic dose

Scope of Changes to E14 Q&As

Q&A 5.1

Double negative nonclinical assessment to support lower clinical exposure needed to waive the positive control

Q&A 6.1

Double negative nonclinical assessment to support an alternative clinical study to show low QTc prolongation risk

Q&A 5.1: Use of Concentration Response Modeling of QTc Data
Q&A 6.1: Alternative Study Designs when a Conventional TQT Study is Not Feasible

Double Negative Nonclinical Assessment

- **When the *in vitro* hERG assay and *in vivo* QT study are conducted using *best practices* and both are negative**
  - Negative hERG assay: hERG safety margin ($^{IC_{50}}/_{C_{max,ss,free}}$) of a new drug is higher than certain threshold calculated based on reference drugs with known TdP risk using the same assay
  - Negative *in vivo* QT study: No significant QT prolongation in animal studies where the investigational drug's exposure (parent and metabolite) covers high clinical exposure. *The level of study sensitivity is different for E14 Q&As 5.1 vs. 6.1.*
    - ***6.1: study has sufficient power to detect a QTc prolongation effect of a magnitude similar to dedicated clinical QT study***

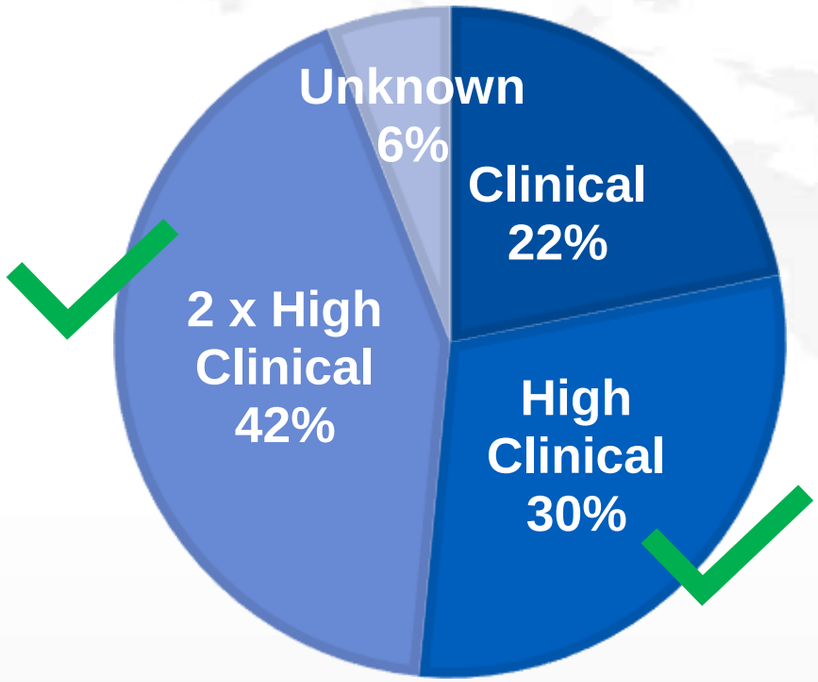
Best Practices are described for hERG Assay in Q&A 2.1 and for *In Vivo* QT study in Q&A 3.1–3.5
Principles to define a double negative integrated nonclinical assessment are described in Q&A 1.1–1.2

Revised Q&A 5.1: Two Pathways to Waive the Positive Control in a Clinical QT Study

- **A separate positive control would not be necessary if either of the following conditions is met:**
  - There are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure

  Or

  - The high clinical exposure scenario has been fully covered in the clinical ECG assessment and nonclinical integrated assessment is <u>double negative</u>



Q&A 5.1 Exposure Margin in QT Reports (FDA, 2016–20)

Example 1: Substitute for TQT Study

- **Sponsor conducted a Single Ascending Dose (SAD) study with high-quality ECGs**
- **The highest dose covers 2-fold the exposure expected when the drug is given with concomitant strong CYP inhibitor (*i.e.*, high clinical exposure scenario)**
- **No evidence of a concentration-response relationship**

Can the SAD study serve as a substitute for a TQT study under Q&A 5.1?

Example 1: Substitute for TQT Study

Answer: Yes

- ✓ Exposures were higher than the high clinical exposure scenario
- ✓ A separate positive control is not necessary because the exposures were 2-fold the high clinical exposure scenario
- ✓ Study included high-quality ECGs

Example 2: Substitute for TQT Study

- **Sponsor conducted a SAD study with high-quality ECGs**
- **The highest dose covers the exposure expected when the drug is given with concomitant strong CYP inhibitor (i.e., high clinical exposure). Exposures are not high enough to waive the positive control.**
- **Nonclinical assessments**
  - hERG safety exposure margin > 100 using best practices for parent compound and major metabolites but without reference drugs
  - No QT signal in dogs at exposures > high clinical exposure scenario, but the study was not powered to detect QT prolongation similar to TQT study

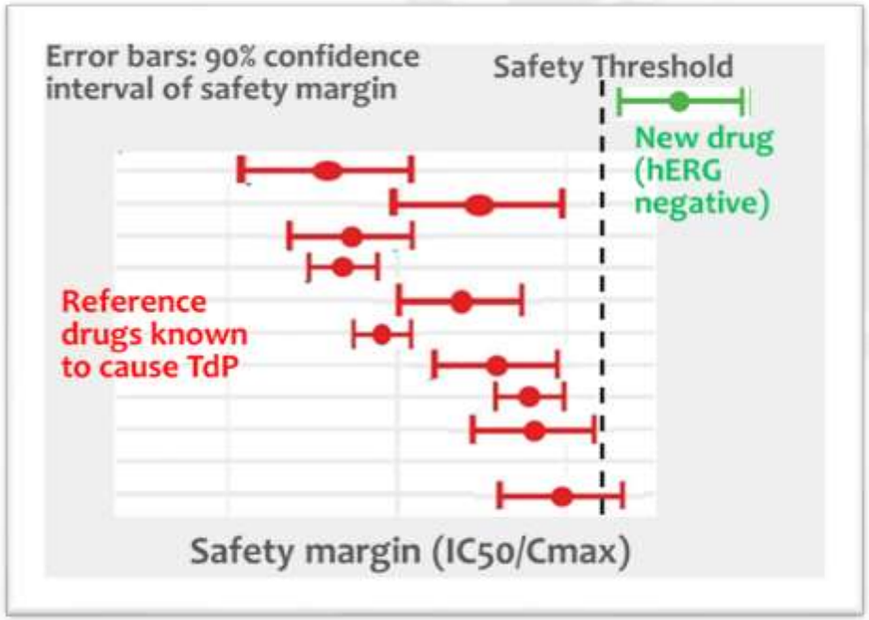
Can the integrated assessment serve as a substitute for a TQT study under Q&A 5.1?

Example 2: Substitute for TQT Study

Answer: No

✗ **The hERG safety margin is not a singular value (i.e., 100 in example). Sponsor will need to show that hERG safety margin > safety margins for reference drugs with known TdP risk using the same assay (S7B Q&A 1.2).**

✓ **In vivo study had exposures exceeding high clinical exposure scenario. The study does not need to be powered to detect QT prolongation similar to TQT study to support 5.1 (S7B Q&A 1.1 and 3.4).**



S7B Q&A 1.2
See Dr. Zhihua Li's presentation for more details.

Scope of Changes to E14 Q&As

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Double negative nonclinical assessment to support lower clinical exposure needed to waive the positive control

Q&A 6.1

Double negative nonclinical assessment to support an alternative clinical study to show low QTc prolongation risk

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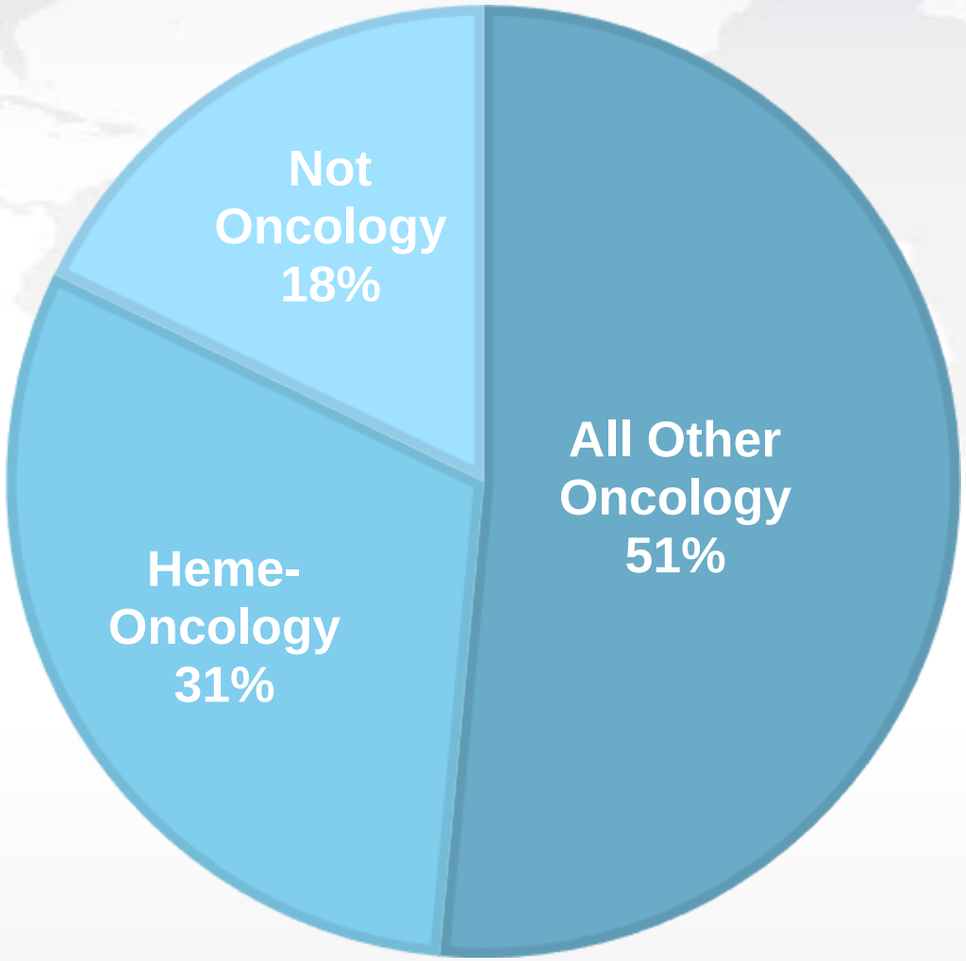
Q&A 6.1: Alternative Study Designs When a Conventional TQT Study is Not Feasible



Q&A 6.1 Indications in QT Reports (FDA, 2016–20)

- **Alternative Study Designs, may include:**
  - Patients
  - No placebo
  - No positive control
  - No supratherapeutic doses
- **Difficult to demonstrate lack of QTc effect**

Revised 6.1: Impact on Decision-Making

To support a drug as having low likelihood of proarrhythmic effects due to delayed repolarization, the assessment should demonstrate 3 criteria:

1) **Double negative nonclinical assessment**
   - hERG safety margins for parent compound and major metabolites under best practice are higher than certain threshold calculated based on reference drugs with known TdP risk using the same assay (S7B Q&A 1.1–1.2)
   - No QTc prolongation in an *in vivo* study of *sufficient power to detect a QTc prolongation effect of a magnitude similar to dedicated clinical QT study* (S7B Q&A 3.4) and exposures > high clinical exposure scenario

Revised 6.1: Impact on Decision-Making (continued)

2) Alternative clinical study

- The high-quality ECG data collected do not suggest QT prolongation, generally defined as ΔQTc less than 10 msec, as computed by the concentration-response analysis or the intersection-union test. The strength of the clinical ECG data depends on the upper bound of the two-sided 90% confidence interval around the mean ΔQTc estimate.
- No notable imbalances between treatment/dose arms in the proportion of subjects exceeding outlier thresholds

3) Cardiac safety database across studies

- Does not suggest increased rate of adverse events that signal potential for proarrhythmic effects

Example 3: Oncology Drug

- **Sponsor conducted an uncontrolled, dose-escalation study with an expansion cohort for an oncology drug in 75 patients. Study included high quality ECGs**
- **The highest dose studied was the labeled dose**
- **No evidence of QTc prolongation using a concentration-response relationship [ΔQTc at $C_{max,ss}$ = 4 (UCL: 8) msec] and no QTc outliers were detected [QTc >480 msec or ΔQTc >60 msec]**
- **No safety pharmacology assessments were conducted according to best practices**

Can the clinical QT assessment support low risk for QTc prolongation under Q&A 6.1?

Example 3: Oncology Drug

Answer: No

- X Nonclinical studies were not conducted under best practice
- X When relying only on the clinical data, there is reluctance to draw conclusions of lack of an effect in an absence of a positive control or large exposure margin
- ➢ Conclude: drug did not cause large mean increases (i.e., 20 msec) in the QTc interval at the therapeutic dose

Example 4: Oncology Drug-2

- **Sponsor conducted an uncontrolled, dose-escalation study with high quality ECGs for an oncology drug in 30 patients**
- **The highest dose studied was the labeled dose**
- **No evidence of QTc prolongation using concentration-response relationship [ΔQTc at $C_{max,ss}$ = 4 (UCL: 12) msec] and no QTc outliers were detected [QTc >480 msec or ΔQTc >60 msec]**
- **Double negative nonclinical assessments using best practices and *in vivo* study was powered to detect QTc prolongation similar to a TQT study.**

Can the integrated QT assessment support low risk for QTc prolongation under Q&A 6.1?

Example 4: Oncology Drug-2

Answer: Yes,
if the cardiac safety database at marketing application does not suggest proarrhythmic risk

- ✓ **Clinical QT study with high quality ECG show no QTc prolongation as defined as ΔQTc < 10 msec and no imbalance of outlier QTc values**
- ✓ **The strength of the clinical ECG data depends on the upper bound of the two-sided 90% confidence interval around the mean ΔQTc estimate**
- ✓ **Double negative nonclinical assessment**

Public Comment

The ICH E14/S7B Implementation Working Group is seeking input *via* public comment on how to define the lack of clinically relevant QT prolongation in the context of the specific #2 criteria above when #1 and #3 would also be met.

- ✓ Double-negative nonclinical assessment (criteria #1)
- ✓ No evidence of proarrhythmia in clinical database (criteria #3)

- Clinical QT study with high quality ECG show no QTc prolongation as defined as ΔQTc < 10 msec and no imbalance of outlier QTc values
- The strength of the clinical ECG data depends on the upper bound of the two-sided 90% confidence interval around the mean ΔQTc estimate and the likelihood of large excursions in plasma concentrations due to intrinsic and/or extrinsic factors that increase bioavailability

Summary of Revised E14 Q&A

Q&A 5.1

Double negative nonclinical assessment to support lower clinical exposure needed to waive the positive control

- **Clinical study should include high-quality ECGs and doses should cover the high clinical exposure scenario**
- **Double negative nonclinical assessment using best practice:**
  - hERG safety margin > reference drugs with same assay
  - *In vivo* QT study evaluated doses covering high clinical exposure scenario

Summary of Revised E14 Q&A

- **Clinical study should include high-quality ECGs and as many elements of TQT study to help reduce variability**
- **Double negative nonclinical assessment using best practice:**
  - hERG safety margin for parent compound and major metabolites > reference drugs with same assay
- ***In vivo* QT study**
  - Covers high clinical exposure scenario
  - Appropriately powered to detect QTc prolongation similar to TQT study

Q&A 6.1

Double negative nonclinical assessment to support an alternative clinical study to show low QTc prolongation risk

ICH
harmonisation for better health

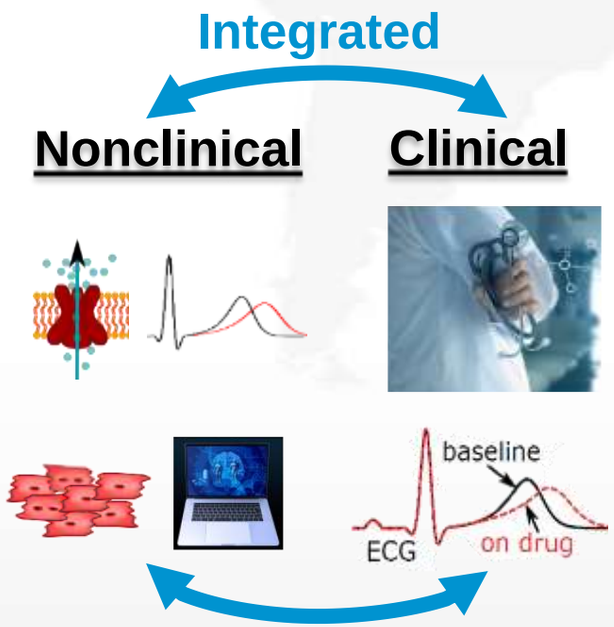
Thank you!

Christine Garnett, PharmD

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Day 1 Schedule

E14 Scenarios and Integrated Risk Assessment



- ✓ **Background, Motivation for and Overview of the New Q&As for ICH E14 and S7B**
  - ✓ **David Strauss, *FDA, United States***
- ✓ **Revised E14 Q&As and Presentation of Examples to Highlight the Impact of Nonclinical Data on Clinical Development and Interpretation**
  - ✓ **Christine Garnett, *FDA, United States***
- ➢ **S7B Integrated Risk Assessment Q&As**
  - o **Zhihua Li, *FDA, United States***
- ➢ **Considerations for an Integrated Nonclinical-Clinical Risk Assessment**
  - o **Jean-Pierre Valentin, *EFPIA***
- ➢ ***Discussion of Questions Received from the Q&A Pod***
  - o **Facilitators: David Strauss, *FDA, United States* and Derek Leishman, *PhRMA***
  - o **All Speakers and Flora Musuamba, *EC, Europe*; Colette Strnadova, *Health Canada, Canada*; Charles Benson, *EFPIA***