



## E14 Q&A(R3) - 5.1: Use of Concentration Response Modeling of QTc Data

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



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## Outline

- **Background**
- **Objective of the Guideline**
- **Scope/Content of the Guideline**
- **Implementation of the Guideline**
- **Conclusion**

## Background

- **Original ICH E14 document**
  - The ICH E14 Guideline states (in Section 3, page 12) that analysis of the relationship between drug concentration and QT/QTc interval changes is under active investigation
- **First Q&A on Concentration Response Modeling issued March 2014 (ICH E14 Q&As\_R2 Question 5.1)**
  - Summarized potential uses for concentration response modeling
  - Did not provide guidance on how concentration response modeling from Phase I studies could be used for regulatory decision making
  - Concluded: “CRR modeling applied on early clinical QT data from healthy volunteers seems promising in terms of enhancing our confidence to characterise QTc prolongation.” [Page 14]

## Background

- **Potential value of ECG assessment in a routinely performed early clinical study to evaluate QTc**
  - Early clinical studies typically achieve the highest plasma levels of the drug in preapproval studies although sample size is small
  - The application of concentration-response modeling provides sufficient power to exclude a QTc increase of 10 milliseconds in a phase 1 study with a typically small sample size
- **IQ-CSRC Study prospectively evaluated 6 drugs using study design similar to Phase I study**
  - 5 drugs with effect on QTc; 1 drug without effect on QTc
  - Use of Concentration Response Modeling correctly identified all 6 compounds

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## Question

**The ICH E14 Guideline states (in Section 3, page 12) that analysis of the relationship between drug concentration and QT/QTc interval changes is under active investigation.**

- **Has this investigation yielded a reasonable approach to concentration-response modeling during drug development?**
- **How can assessment of the concentration-response relationship guide the interpretation of QTc data?**

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## Objective of Q&A 5.1

- **ICH E14 Q&As R3 published December 2015**
  - Updated Q&A 5.1 on use of concentration response modeling
  - Incorporates use of concentration response modeling of Phase I data for regulatory decision making
- **Objectives**
  - Describe the evaluation of the effect of a drug on QTc across range of concentrations using concentration response modeling
  - Establish guidelines for regulatory decision making using concentration response modeling (in contrast to the intersection union test described in ICH E14)

## Scope/Content of Guideline

- **Concentration-response analysis can serve as an alternative to the by-time-point analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug.**
- **In either case this result is an important component of the totality of evidence assessment of the risk of QT prolongation.**
  - includes nonclinical data
  - the time course of QT prolongation
  - the magnitude of QT prolongation
  - categorical analyses of outliers
  - certain adverse events in patients that can signal potential proarrhythmic effects.

## Approach to Modeling Concentration Response Data

- **There are many different types of models for the analysis of concentration-response data**
  - descriptive pharmacodynamic (PD) models (e.g., linear or Emax models), or empirical models that link pharmacokinetic (PK) models (dose-concentration-response) with PD models.
- **In order to limit bias, prior to analysis, it is important to specify**
  - modeling methods and assumptions
  - criteria for model selection
  - rationale for model components
  - potential for pooling of data across studies

## Approach to Modeling Concentration Response Data

- **Prospective specification of model characteristics based on knowledge of the pharmacology is recommended whenever possible including**
  - structural model
  - objective criteria
  - goodness of fit
- **Testing for model assumptions, hysteresis (a plot of data by-time point and a hysteresis loop plot), and goodness of fit should be documented.**

## Approach to Modeling Concentration Response Data

- **On occasion, the QT effect is not a direct function of plasma concentration.**
  - drugs that cause QT prolongation as a result of changes in protein synthesis or trafficking
  - drugs with accumulation into myocardial tissues might demonstrate hysteresis.
- **Concentration-response analysis can be challenging when more than one molecular entity (multiple drugs or parent plus metabolites) contributes to the QTc effect.**

## Important considerations

1. **Concentration-response data need not come from a dedicated QT study, nor even a single study, but there are several new and important considerations.**
  - Data can be acquired from first-in-human studies, multiple-ascending dose studies, or other studies.
  - Additional data would be useful to ensure information on exposure well above the exposure at the maximum therapeutic dose, to cover the impact of accumulation with repeated dosing, drug-drug and drug-food interactions, organ dysfunction, or genetically impaired metabolism.
  - It is anticipated that one would collect new data to add to previous data, if appropriate, rather than using new data for independent analyses.

## Important considerations

- 2. Efficient concentration-response analysis requires as much quality control as is needed for a dedicated study.**
  - Includes robust, high-quality Electrocardiogram (ECG) recording and analysis sufficient to support a valid assay for ECG intervals (see E14 and Q&A #1).
- 3. If there is an intention to pool data from multiple studies, it is important to test for heterogeneity.**
- 4. If there are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure (see E14 section 2.2.2), a separate positive control would not be necessary.**

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## Decision-making

- **Both the intersection-union test and the concentration-response analysis can estimate the maximum effect of a drug treatment on the QTc interval, but they are not used to test the same hypothesis.**
  - Inspection of the time course of QT prolongation is important.
  - However, hypothesis testing based on a by-time point analysis (intersection-union test or point estimate and confidence intervals) is inappropriate in studies designed for a concentration-response analysis, if not powered to assess the magnitude of QT prolongation for each time point.

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## Decision-making

- **When using a concentration-response analysis as the primary basis for decisions to classify the risk of a drug**
  - the upper bound of the two-sided 90% confidence interval for the QTc effect of a drug treatment as estimated by exposure-response analysis should be <10 ms at the highest clinically relevant exposure to conclude that an expanded ECG safety evaluation during later stages of drug development is not needed. (See E14, section 2.2.4 and Q&A #7).

## Other uses

- **Concentration-response analysis has established its utility in several settings enumerated below**
  - Predicting the QT effects of doses, dosing regimens, routes of administration, or formulations that were not studied directly. Interpolation within the range of concentrations studied is more reliable than extrapolation above the range.
  - Understanding the concentration-response relationship can help predict the effects of intrinsic (e.g., cytochrome P450 isoenzyme status) or extrinsic (e.g., drug-drug PK interactions) factors on the QTc interval, possibly affecting inclusion criteria or dosing adjustments in later phase studies.



**Thank You!**

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