ICH E14/S7B Q&As (R1)

Step 4 document – to be implemented

Date 20 August 2026

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Background

- **The training materials are linked to the revised ICH E14/S7B Q&As approved in August 2026**
- **The training materials should be used in conjunction with the training materials linked to ICH E14/S7B Q&As approved in March 2022**
- **Under certain circumstances the current August 2026 Q&As modify the approach outlined in the March 2022 Q&As**

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ICH S7B Q&A Changes

- **Scope of ICH S7B has been broadened to match ICH S7A and ICH E14, this makes ICH S7B relevant for a wider range of modalities (ICH S7B Q&A 1.1)**
- **The possibility of using qualified alternative assays instead of the standard *in vitro* hERG and *in vivo* QTc assessment, has been added as a new Q&A (ICH S7B Q&A 1.5)**
- **It is recommended, when feasible, to use ECGs from repeat dose toxicology studies for the QTc assessment instead of conducting a standalone *in vivo* QT study (ICH S7B Q&A 3.6)**
- **A framework to determine the most appropriate nonclinical testing paradigm has been added as a new Q&A (ICH S7B Q&A 1.4)**
- **Existing ICH S7B Q&As on integrated assessment and ICH E14 Q&As 5.1, 6.1 and 6.3 (see slide 9) have been modified to reflect the additional ICH S7B Q&As**

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Framework for Selecting an Informative ICH S7B Strategy

ICH S7B Q&A 1.4 enables the use of a rational and risk-based framework to guide nonclinical testing strategies. The framework integrates information about known risk factors and the totality of evidence associated with a new drug or modality. This approach promotes a fit-for-purpose (flexible) and evidence-based nonclinical risk testing strategy to evaluate hERG block-mediated ventricular repolarisation risk. This nonclinical framework can also inform clinical QTc evaluation needs.

Factors To Consider

- **Physicochemical properties**
  - Does this drug candidate have physicochemical properties associated with membrane permeability and/or hERG inhibition?
- **Mechanistic plausibility**
  - Has the modality demonstrated the ability to directly inhibit hERG function (off-target)?
- **Accrued Evidence**
  - Is this drug candidate associated with a pharmacological or chemical class with known QTc prolongation risk based on prior nonclinical, clinical or post-marketing evidence?

Physicochemical properties, mechanistic plausibility and accrued evidence should be interpreted together to inform risk and guide the appropriate ICH S7B testing strategy

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Physicochemical Properties Associated with Direct hERG Interaction

Non-exhaustive List of Factors Informing the Likelihood of Delayed Ventricular Repolarisation

Physicochemical Feature	"Likely"	"Not likely"	References
Modality Example	Small molecules	Monoclonal antibodies & large proteins	1,2,3
Molecular size & conformational flexibility (molecular weight, length, rotatable bonds, etc)	Low molecular weight; conformational flexibility enables interaction with multiple binding sites	High molecular weight; ordered structural elements (e.g., helices, folding, rigid domains, disulfide linkers, loops) with conformational complexity	4,5,6,7,8
Membrane permeability (e.g., cLog P, pKa, polarity)	Passive diffusion and/or active uptake	Minimal or absent permeability	4,5,6
Pharmacophore hydrophobicity & aromaticity (hydrophobic centers, lipophilic, cation–π interactions, etc)	Higher lipophilicity	Highly hydrophilic	5,9,10
Charge characteristics (protonatable nitrogen, proximity to aromatic group, etc.)	Basic amine with positive charge or cationic functionalities	Highly negatively charged or polyanionic	5, 9,10

Key Messages

- "Likely" modalities have essential physicochemical properties that permit membrane permeability and binding to critical amino acids in the hERG pore.
- "Not likely" modalities have restricted cardiomyocyte membrane permeability and low potential for hERG binding based on physicochemical attributes.

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Mechanistic Plausibility for Direct hERG Interaction

Mechanistic plausibility refers to the biological feasibility that a modality can directly block the hERG channels and thereby contribute to delayed ventricular repolarisation. Mechanistic plausibility is informed by both the known behavior of a drug class and the ability of a modality to access and interact with the intracellular hERG binding site.

- **Drug Class / Modality Characteristics**
  - Mechanistic plausibility is strengthened when a drug class has been clearly associated with direct hERG block and when the underlying mechanism is well characterised (e.g., small molecules; 5).
  - Mechanistic plausibility is diminished when a modality has not been associated with direct hERG block and no biologically plausible mechanism for channel block has been established (e.g., mAb, large proteins; 11-12).
- **Ability to Access the hERG Central Pore**
  - Direct hERG block requires binding to amino acid residues within the intracellular central pore of the channel. Small molecules often permeate cardiomyocyte membranes and enter the channel (open state) to inhibit function.
  - Some larger molecules (non-small molecules) cannot cross the cell membrane to reach the common drug-binding sites on hERG because of their physicochemical properties (e.g., mAb, large proteins; 5, 13). As a result, hERG block is unlikely.

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Accrued Evidence

Contribution to Inform the Likelihood of hERG-mediated Delayed Ventricular Repolarisation

Accrued evidence refers generally to all sources of available evidence that can be used to support a weight of evidence evaluation of hERG-mediated QTc prolongation risk for a new modality. Accrued evidence represents the growing body of facts that accumulates, builds up or becomes available over time and can be used to support classification of a new modality as either likely or not-likely.

Accrued evidence can emerge from various sources, including (but not limited to):

- Publications: Peer-reviewed datasets that compiled nonclinical and clinical QTc evidence for a given modality.
- Public-domain datasets (e.g., evidence shared at scientific conferences, meetings, consortia, etc.).
- Sponsor-derived datasets on proprietary molecules that may or may not be available in public domain.

Re-assignment of Risk Categories for New or Emerging Modalities:

- Q&A 1.4: Modalities could be reassigned from “unknown” to “not-likely” or “likely” regarding their potential for delayed ventricular repolarisation through direct hERG interaction based on integrated assessment of physicochemical properties, mechanistic plausibility, and accrued evidence.

We encourage publication of data whenever possible, especially for new or emerging modalities

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ICH E14 Q&A Changes

E14 Q&A 5.1 — Concentration-Response as Primary Basis

- "Positive control not necessary" condition (b) now references the S7B Q&A 1.4 modality framework rather than naming hERG and in vivo QT specifically.
- Decision thresholds unchanged, evidence pathways broader.

E14 Q&A 6.1 — When a Thorough QT Study is Not Feasible.

- Nonclinical evidence requirement now references "the testing strategy in S7B Q&A 1.4 parts (b) and (c)" rather than naming hERG and in vivo QT specifically.
- Decision thresholds unchanged, evidence pathways broader

E14 Q&A 6.3 — Novel Modality Exemption from Thorough QT

- Expanded beyond “large proteins and monoclonal antibodies” to therapeutic modalities (non-small molecules) where hERG interaction is not likely per S7B Q&A 1.4 part (a)

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Integrated Testing Paradigm Considerations

S7B or E14 Assay	Regulatory Compliance	Likely	Unknown	Not Likely
In vitro hERG or qualified alternative assay	ICH S7B Q&As 1.2, 2.1, 1.5	√	√	-
In vivo QTc assessment or qualified alternative assay	ICH S7B Q&As 3.1-3.6, 1.5	√	√	-
Clinical QTc assessment	ICH E14; ICH E14 Q&As 5.1 or 6.1	√	√	*

* *See E14 Q&A 6.3*

Exemption from a dedicated QTc assessment under the Q&As does not eliminate the need for safety ECG collection in clinical trials; standard safety ECG monitoring remains an expected component of a clinical development program.

Legend: core (√); no testing or not applicable (-)

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