“Preclinical Perspectives of QT – Outlook from ICH Guidelines”
Biometry in Early Clinical Research QT/QTc-Interval

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Safety Pharmacology and ICH

- 1995 - ICH M3 states that “safety pharmacology .. should be [done] prior to human exposure”
  - refers in general terms to “effects on vital functions such as cv, cns and respiratory systems”

- 1999 - ICH adopts safety pharmacology as a topic, S7(A)
- 2000 - final guideline signed off
- 2001 - ICH S7A implemented
- 2002 - ICH S7B Step 2 / 3
- 2003 back to Step 2 due to E14
- 2005: Step 4
COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER:
THE ASSESSMENT OF THE POTENTIAL FOR QT INTERVAL PROLONGATION BY NON-CARDIOVASCULAR MEDICINAL PRODUCTS
Scope of the Guidelines S7A + S7B

Safety Pharmacology studies should be carried out for:

- new chemical entities
- biotechnology-derived products, when appropriate
- previously approved pharmaceuticals, when appropriate

  e.g. when a new patient population or a new route of administration raises new concerns
Core Battery /Cardiovascular System/ S7A

- Assess appropriately:
  - blood pressure
  - heart rate
  - electro-cardiogram

- Consider also:
  - in vivo, in vitro and/or ex vivo evaluations, including methods for repolarization and conductance abnormalities
Background for S7B

In the past, industry has:

- measured blood pressure and heart rate
- recorded ECG (generally limb leads) in Safety Pharmacology and Toxicology studies
- looked for disturbances of rhythm
- measured intervals and amplitudes, including QT, in Lead II
- corrected QT for heart rate (usually by Bazett’s formula!)
Regulatory concerns

- Increasing awareness that non-cardioactive drugs, used for sometimes non-life threatening diseases, can cause QT prolongation and serious dysrhythmias such as TdP.

- In 1997 CPMP issued a Points to Consider document (CPMP/986/96) that recommended additional non-clinical (and clinical) tests.
Literature informing about QT Prolongation

- 71 Compounds identified (not exhaustive):
  - Antiarrhythmics (15)
  - Histamine receptor antagonists (11)
  - Ion channel antagonists (8)
  - Antidepressants / psychiatric (15)
  - Antibiotics (5)
  - Other (17)
    - Peptides, Immunosuppressants, Hypolipidemicals, Antimalarial
Industry reaction

- Internal debate
- Status of a “Points to Consider” document
  - need to comply
  - scientific justification
- Decision taken to generate \textit{in vitro} electrophysiology data to support FTIH studies
  - dog isolated Purkinje fibre
Assay problems

- Decided to analyse concentration of compound in perfusate used in Purkinje fibre studies

- Found, for some compounds (approximately 50%), that there was a “loss” of compound during passage through apparatus
  - not predictable
  - binding to glass
  - instability (37°C)
What to do with a positive result

- Case-by-case analysis

- Positive non-clinical findings do not necessarily kill a compound

- They are, however, likely to result in something in the labelling

- Outcome depends on severity of label and intended indication, position in market etc
The QT Interval
Background

- The QT interval (time from the beginning of the QRS complex to the end of the T wave) of the electrocardiogram (ECG) is a measure of the duration of ventricular depolarization and repolarization.

- QT interval prolongation can be congenital or acquired (e.g., pharmaceutical-induced).

- When the QT interval is prolonged, there is an increased risk of ventricular tachyarrhythmia, including torsade de pointes, particularly when combined with other risk factors (e.g., hypokalemia, structural heart disease, bradycardia).
Scope of the Guideline S7B

- This nonclinical guideline extends and complements the “ICH Guideline on Safety Pharmacology Studies for Human Pharmaceuticals” (ICH S7A).

- This guideline generally applies to new chemical entities for human use.

- This guideline can be applied to marketed pharmaceuticals when appropriate (e.g. when adverse clinical events, a new patient population, or a new route of administration raises concerns not previously addressed).

- Principles and recommendations concerning study design and conduct as described in ICH S7A also apply to the studies in the present guideline.
General Principles of S7B

- The choice of assays and data used to identify the hazard of QT interval prolongation for a test substance should be scientifically based.

- *In vitro* and *in vivo* assays are complementary approaches; therefore, according to current understanding, more than one type of assay should be conducted.
General Considerations for Selection and Design of Studies

Nonclinical methodologies can address four electrophysiological levels of integration that can manifest as delayed ventricular repolarization and potential sequelae. These levels include:

- **Ionic currents** measured in isolated animal or human cardiac myocytes, cultured cardiac cell lines, or heterologous expression systems for cloned human ion channels.

- **Action potential** parameters in isolated cardiac preparations or specific electrophysiology parameters indicative of action potential duration in anesthetized animals

- **ECG** parameters measured in conscious or anesthetized animals.

- **Proarrhythmic effects** measured in isolated cardiac preparations or animals.
General Considerations for Selection and Design of Studies

- *In vitro* electrophysiology studies can explore potential cellular mechanisms that may not be evident from *in vivo* data.

- Changes in other cardiovascular parameters or effects on multiple ion channels can complicate interpretation of data.

- Complementary assessments in other systems can address this issue. While inhibition of $I_{Kr}$ is thought to be the most common mechanism responsible for pharmaceutical-induced prolongation of QT interval in humans, delay of repolarization through actions on other ion channels is possible.
General Nonclinical Testing Strategy

- The following section describes a general nonclinical testing strategy for assessing evidence of risk for QT interval prolongation that is pragmatic and based on currently available information.

- The figure illustrates the component elements of the testing strategy, but not specific test systems or their designs.
ICH/S7B Nonclinical Testing Strategy / QT / Step 4

Nonclinical Testing Strategy

- In Vitro $I_{Kr}$ Assay
- In Vivo QT Assay

Integrated Risk Assessment

Follow-up Studies

Evidence of Risk

Chemical/Pharmacological Class

Relevant Nonclinical and Clinical Information
Can you exclude any risk for QT-Prolongation
Introduction to hERG, QT Interval Prolongation and Torsades de Pointes

• The $I_{Kr}$ – hERG link

Potassium channel $\alpha$-sub-units encoded for by human ether-a-go-go-related gene (hERG)

Current = $I_{Kr}$
ICH/S7B Nonclinical Testing Strategy

Chemical/pharmacological class

Consideration should be given to whether the test substance belongs to a chemical/pharmacological class in which some members have been shown to induce QT interval prolongation in humans (e.g., antipsychotics, histamine H-1 receptor antagonists, fluoroquinolones). This should, where appropriate, influence the choice of reference compound(s) and be included in the integrated risk assessment.
Relevant nonclinical and clinical Information for the integrated risk assessment
from:

- Pharmacodynamic studies,
- Toxicology/safety studies,
- Pharmacokinetic studies, including plasma levels of parent substance and metabolites (including human data if available),
- Drug interaction studies,
- Tissue distribution and accumulation studies,
- Post-marketing surveillance.
Follow-up Studies, Options:

- Use of ventricular repolarization assays that measure action potential parameters in isolated cardiac preparations

- Use of specific electrophysiological parameters indicative of action potential duration in anesthetized animals

- Repeated administration of test substance,

- Selection of animal species and gender(s),
Follow-up Studies

- Use of **metabolic inducers or inhibitors**, 
- Use of **concurrent positive control** substances and reference compounds, 
- Inhibition of other channels not previously evaluated, 
- Measurement of electrophysiological parameters at **multiple time points**, 
- **Confounding effects** in conscious animals that limit the interpretation of data such as test substance-induced effects on heart rate or autonomic tone, or toxicities such as tremor, convulsion, or emesis.
Integrated risk assessment (IRA)

- Evaluation of non-clinical study results including the results from follow-up studies and other relevant information.

- Should be scientifically based and individualized for the test substance.

- Such an assessment can contribute to the design of clinical investigations and interpretation of their results.

- IRA should be provided for the Investigator’s Brochure and the Nonclinical Overview (ICH M4).
The integrated risk assessment should also consider:

- **Potencies** of test substance in S7B assays relative to reference compound(s),

- **Safety margins** from *in vivo* QT assays,

- **Assay sensitivity** and specificity,

- Contribution of **metabolites** to QT interval prolongation as well as metabolic differences between humans and animals.
Evidence of Risk

Evidence of risk is the overall conclusion from the integrated risk assessment for a test substance to delay ventricular repolarization and prolong QT interval in humans.
Use of **positive** control substances and reference compounds

- Positive control substances should be used to establish the sensitivity of *in vitro* preparations for ion channel and action potential duration assays.
- In the case of *in vivo* studies, positive control substances should be used to validate and define the sensitivity of the test system, but need not be included in every experiment.
- For test substances belonging to a chemical/pharmacological class that is associated with QT interval prolongation in humans,
  - the use of concurrent reference compound(s) (member(s) of the same class) in *in vitro* and *in vivo* studies should be considered to facilitate ranking the potency of the test substance in relation to its comparators.
- Whether or not positive control substances or reference compounds are used in experiments should be justified.
Species for In-vitro electrophysiology studies

Tissue and cell preparations for in vitro assays are obtained from different laboratory animal species including rabbit, ferret, guinea pig, dog, swine, and occasionally from humans.

The ionic mechanisms of repolarization in adult rats and mice differ from larger species, including humans (the primary ion currents controlling repolarization in adult rats and mice is $I_{to}$); therefore, use of tissues from these species is not considered appropriate.
Factors that can confound or limit the interpretation of in vitro electrophysiology studies include the following:

- The testing of high concentrations of the test substance can be precluded by limited solubility in aqueous physiological salt solutions,

- **Adsorption to glass** or plastic or non-specific binding to the test matrix can reduce the concentration of the test substance in the incubation or perfusion medium,

- Test substance concentrations can be limited by cytotoxic or physicochemical attributes of the test substance that disrupt cell membrane integrity so that electrophysiological endpoints cannot be obtained,
QT Interval Correction

*In vivo* electrophysiology studies

- When the effects are due to test substances, the most common approach is to correct the QT interval for heart rate (QTc) using formulae such as **Bazett** or **Fridericia**; however, these corrections can yield misleading data, especially when differences in heart rate between treatment and control are large. An alternative approach is to maintain a constant heart rate using cardiac pacing.
<table>
<thead>
<tr>
<th></th>
<th>Bazett</th>
<th>Fridericia</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc = QT/√2 RR</td>
<td>QTc = QT/√3 RR</td>
<td></td>
</tr>
<tr>
<td>QT</td>
<td>420 msec</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>72 beats/min</td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td>460 msec</td>
<td>446 msec</td>
</tr>
</tbody>
</table>

Bazett’s formula tends to overcorrect high heart rates and under corrects low heart rates. Even though Bazett’s formula is more often used for correction of human QT intervals (Bonate and Russell, 1999).
Taking into account that heart rate in canine is higher as in humans using the Bazett formula will overcorrect QT in canine ECG. This can be shown with ECG data taken from Osborne and Leach (1971).

As heart rate increases, QT decreases and QTc increases.
NONCLINICAL DATA TO SUPPORT ICH S7B

SOURCES OF DATA

* ILSI/HESI Non-Clinical CV Studies Subcommittee
  Prospective studies with 12 drugs
  Participation by PhRMA, EFPIA, JPMA, FDA, Academic

* ICH S7B Data Survey
  Retrospective call for data with 54 drugs
  Contributions from PhRMA, EFPIA and JPMA Companies
  Data from published literature

* QT PRODACT (JPMA)
  Prospective studies with 22 drugs
  Participation by JPMA Companies and Contract Labs
ICH S7B Data Collection Initiatives

In Vitro $I_{Kr}$ Assay (hERG)

Summary of Findings
1. Assay results among laboratories are consistent.
2. Almost all drugs that prolong QT in humans inhibit hERG.
3. Of drugs that do not prolong QT in humans, 50-90% inhibit hERG at large concentrations.

Conclusions
1. hERG assay is useful as a core or follow-up assay.
2. Concentration (potency) of hERG inhibition should be considered in integrated risk assessment.
ICH S7B Data Collection Initiatives

Repolarization Assay (APD)

Summary of Findings

1. Variable results among preparations.
   - Some QT positive drugs not captured by \( \text{APD}_{90} \) Purkinje fibre assay.
   - Guinea pig papillary muscle assay has better sensitivity than Purkinje fibre assay

2. When activity is observed, valuable information can be obtained to further characterize risk.
Conclusions
1. APD$_{90}$ Purkinje fibre assay of low value for excluding risk.
2. APD assay is useful as Follow-Up Assay
3. Other repolarization assays are under consideration
ICH S7B Data Collection Initiatives

In Vivo QT Assay

Summary of Findings

★ With standardization of protocols and use of positive controls, results among assays and laboratories are consistent.

★ Of drugs tested that prolong QT interval in humans, they were positive in In Vivo QT Assays in almost all laboratories.

Conclusions

★ In Vivo QT Assay should be a core assay.
★ Combined QT assessment and pharmacokinetic data are most valuable.
Timing of S7B Non-clinical Studies and Integrated Risk Assessment in Relation to Clinical Development / Step 4, June 2005, Brussels

- Conduct of S7B non-clinical studies assessing the risk for delayed ventricular repolarization and QT interval prolongation prior to first administration in humans should be considered.

- These results, as part of an integrated risk assessment, can support the planning and interpretation of subsequent clinical studies.
The Clinical E14 Draft Guideline

In parallel with the nonclinical S7B Guideline, a clinical Guideline was prepared – E14

This document recommends a clinical study designed to specifically investigate the potential of a compound to prolong QTc

- The “thorough QTc (TQT) study”
### Clinical/Nonclinical Correlation

Clinical: ≤ 5 msec (mean change-placebo)

<table>
<thead>
<tr>
<th>hERG cutoff</th>
<th>False Positives (hERG)</th>
<th>False Positive (in vivo)</th>
<th>False Positive (hERG or in vivo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 µM</td>
<td>≤ 10 µM ≤ 50 µM</td>
<td>≤ 1 µM ≤ 10 µM ≤ 50 µM</td>
<td>(+10%, SS) ≤ 1 µM ≤ 10 µM ≤ 50 µM</td>
</tr>
</tbody>
</table>

#### Drug Results

- **Drug 1**: negative, positive, positive - 2 of 9, 6 of 9, 7 of 9 - negative, 1 of 7, 2 of 9, 6 of 9, 7 of 9
- **Drug 2**: negative, positive, positive - negative
- **Drug 3**: negative, positive, positive - negative
- **Drug 4**: positive, positive, positive - negative
- **Drug 5**: positive, positive, positive - positive
- **Drug 6**: negative, positive, positive - negative
- **Drug 7**: negative, negative, negative - no data
- **Drug 8**: negative, negative, negative - negative
- **Drug 9**: negative, negative, positive - no data
### “FDA Comparison of Preclinical and Clinical Data”

#### Clinical: > 5 to < 10 msec (mean change-placebo)

<table>
<thead>
<tr>
<th>hERG cutoff</th>
<th>False Negatives (hERG)</th>
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<th>False Negatives (hERG or in vivo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 µM</td>
<td>≤ 10 µM</td>
<td>≤ 50 µM</td>
<td>(+10%, SS)</td>
</tr>
<tr>
<td>Drug 10</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Drug 11</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Drug 12</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
</tr>
</tbody>
</table>

#### Clinical: ≥ 10 to < 20 msec (mean change-placebo)

<table>
<thead>
<tr>
<th>hERG cutoff</th>
<th>False Negatives (hERG)</th>
<th>False Negatives (in vivo)</th>
<th>False Negatives (hERG or in vivo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 µM</td>
<td>≤ 10 µM</td>
<td>≤ 50 µM</td>
<td>(+10%, SS)</td>
</tr>
<tr>
<td>Drug 13</td>
<td>negative</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Drug 14</td>
<td>negative</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Drug 15</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Drug 16</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>Drug 17</td>
<td>positive</td>
<td>positive</td>
<td>negative</td>
</tr>
</tbody>
</table>

#### Clinical: ≥ 20 msec (mean change-placebo)

<table>
<thead>
<tr>
<th>hERG cutoff</th>
<th>False Negatives (hERG)</th>
<th>False Negatives (in vivo)</th>
<th>False Negatives (hERG or in vivo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 µM</td>
<td>≤ 10 µM</td>
<td>≤ 50 µM</td>
<td>(+10%, SS)</td>
</tr>
<tr>
<td>Drug 18</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Drug 19</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
</tr>
</tbody>
</table>
Conclusions

- S7B proposes a series of nonclinical tests which it is believed can predict the likelihood that a compound will prolong cardiac repolarisation \textit{in vivo}, in animals and in humans.

- These data currently have little impact on the clinical development proposals contained in the draft E14 guideline.