Safety Pharmacology
ICH S 7 A + B Guidelines

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ICH Guideline M 3
Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

"Safety pharmacology includes the assessment of effects on vital functions, such as cardiovascular, central nervous and respiratory systems, and these should be evaluated prior to human exposure. These evaluations may be conducted as additions to toxicity studies or as separate studies."
"The aim of the safety pharmacology studies should be to reveal any functional effects on the major physiological systems e.g.: cardiovascular, respiratory, renal, and central nervous systems."
ICH S7A
SAFETY PHARMACOLOGY STUDIES
FOR HUMAN PHARMACEUTICALS

ICH Step 5

NOTE FOR GUIDANCE ON SAFETY PHARMACOLOGY STUDIES
FOR HUMAN PHARMACEUTICALS
(CPMP/ICH/539/00)

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<th>TRANSMISSION TO CPMP</th>
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SAFETY PHARMACOLOGY

Definitions

❖ Primary pharmacodynamic effects (Note 2)
  • studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target.

❖ Secondary pharmacodynamic effects (Note 2)
  • studies of the mode of action and/or effects of a substance not related to its desired therapeutic target.

❖ Safety pharmacology
  • studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above.
SAFETY PHARMACOLOGY

Objectives of Studies

• **Identify** undesirable pharmacodynamic properties relevant to human safety

• **Evaluate** adverse pharmacodynamic and/or patho-physiological effects observed in toxicology and/or clinical studies

• **Investigate** the mechanism of the adverse pharmacodynamic effects
demonstrate the presence of an effect

- negative and positive control groups should be included

- in well-characterized in vivo test systems, positive controls may not be necessary
1. Doses should include and exceed the primary pharmacodynamic or therapeutic range.

2. **High Dose**: should produce moderate adverse effects in this or in other studies of similar route and duration.

3. These adverse effects can include dose-limiting pharmaco-dynamic effects or other toxicity. (e.g. tremors or fasciculations during ECG recording)
Core Battery a must

Studies conducted as necessary

- Follow-up Studies for Core Safety Pharmacology Battery
- Supplemental Safety Pharmacology Studies
<table>
<thead>
<tr>
<th>Safety Pharmacology</th>
<th>Examples of adverse reactions</th>
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<td>Central Nervous System</td>
<td>Convulsion, disturbance of consciousness, etc.</td>
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<tr>
<td>Cardiovascular Functions</td>
<td>Arrhythmia, circulatory shock, etc.</td>
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<tr>
<td>Respiratory Functions</td>
<td>Bronchospasm, respiratory failure, etc.</td>
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Core Battery / Vital Functions (3)

- Cardiovascular System
  - Blood pressure
  - Heart rate
  - Electrocardiogram
  - *In vivo, in vitro* and/or *ex vivo* evaluations, including methods for repolarization and conductance abnormalities should be considered.
SAFETY PHARMACOLOGY

Timing of Studies

Prior to First Administration in Humans

Core battery, follow-up or supplemental studies based on a cause for concern

During Clinical Development

To clarify observed or suspected undesirable effects in animals and humans.

Before Approval

- Supplemental studies unless not warranted
- SP endpoints covered in other studies
SAFETY PHARMACOLOGY

GLP = Good Laboratory Practice

❖ GLP obligatory
  • Core battery
  • SP endpoints from toxicology studies
  • Secondary PD studies when pivotal

❖ GLP to the greatest extent feasible for
  • Supplemental, follow-up

❖ NOT GLP
  • Primary PD studies
  • Secondary PD when not pivotal
ICH S7B Guideline:

The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

CPMP/ ICH/ 423/05/ Step 5
71 Compounds identified
(not exhaustive):
- Antiarrhythmics (15)
- Histamine receptor antagonists (11)
- Ion channel antagonists (8)
- Antidepressants / psychiatric (15)
- Antibiotics (5)
- Other (17)
  - Peptides, Immunosuppressants, Hypolipidemics, Antimalarials
• 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).
General Considerations for Selection of Studies

4 electrophysiological levels can lead to delayed ventricular repolarization:

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

- 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.
The Normal Electrocardiogram

**Risk factors:**
- ion channel mutations
- hypokalemia
- bradycardia, etc

**APD prolongation and early after depolarization (EAD)**

**QT prolongation**

**+ Risk factors:**
- ion channel mutations
- hypokalemia
- bradycardia, etc

**Torsades de pointes**
Importance of hERG

• hERG is major repolarization channel
• hERG is most frequent cause for cardiac side effects
• Interaction with other cardiac channels less frequent
Mechanism of Drug-Induced block of HERG-Channel

(Tristani - Firouzi et. al. 2001)
Objective of the Guideline S7B

• Nonclinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization

• Information concerning nonclinical assays and an integrated risk assessment = Evidence
General Principles

• Principles and recommendations described in ICH S7A also apply to S7B studies.
• *In vitro* and *in vivo* assays are *complementary* approaches; therefore, both assay types should be conducted.
• The investigational approach and evidence of risk should be *individualized* for the test substance, depending on its
  • pharmacodynamic,
  • pharmacokinetic and
  • safety profiles.
ICH/S7B: Nonclinical Testing Strategy

- In Vitro $I_{kr}$ assay
- In Vivo QT assay
- Chemical/Pharmacological Class

Follow-up Studies

Integrated Risk Assessment

Evidence of Risk

Relevant Nonclinical and Clinical Information
Nonclinical Testing Strategy

1. **In vitro** $I_{kr}$ assay
   Effects on $I_{Kr}$ or the ionic current through a native or expressed $I_{Kr}$ channel protein, such as that encoded by hERG

2. **In vivo** QT assay (ECG)
   Measures indices of ventricular repolarization such as QT interval

3. Chemical/pharmacological class (Literature etc.)
   Consider chemical/pharmacological class if some members of class have been shown to induce QT interval prolongation in humans (e.g., antipsychotics, histamine H-1 receptor antagonists, fluoroquinolones).
   This should influence the choice of reference compound(s) and be included in the integrated risk assessment.
Relevant nonclinical and clinical Information

• Additional information for the integrated risk assessment can include results 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 should provide greater depth of understanding for delayed ventricular repolarization and QT interval prolongation in humans.

Such studies can provide additional information on potency, mechanism of action, slope of the dose-response curve, or magnitude of the response.

For Follow-up studies various *in vivo* or *in vitro* study designs can be applicable.
Follow-up Studies

• 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),
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 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.
ICH S7B Data Collection Initiatives

**Repolarization Assay (APD)** (cont.)

Conclusions

1. $\text{APD}_{90}$ 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.
The integrated risk assessment evaluates the non-clinical study results.

The IRA should be scientifically based and individualized for the test substance.

IRA 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).
Integrated Risk Assessment

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

- Safety margins from *in vivo* QT assays,

- Assay sensitivity and specificity,

- Role of metabolites for QT interval prolongation and metabolic differences between humans and animals.
Safety Margins

- Relationship between the exposures associated with an effect on repolarization and those eliciting the primary pharmacodynamic effect in the non-clinical test species or the proposed therapeutic effect in humans
Evidence of Risk

Evidence of risk is the **Overall Conclusion** from the integrated risk assessment for a test substance to delay ventricular repolarization and to prolong QT interval in humans.
Timing of S7B Non-clinical Studies in Relation to Clinical Development / Step 5, 2005:

• 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.
ICH S7B & E14 Guidelines
Step 5, 2005

S7B Guideline
The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

E14 Guideline
The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes

www.Torsades.org
(Updated April 10, 2001). Please check our website, www.Torsades.org for the most current information.
Raymond L. Woosley, MD, Ph.D.
www.GeorgetownCERT.org

Information from the FDA-approved drug labeling and the medical literature.

- **QT**: prolongation is mentioned in the FDA-approved labeling as a known action of the drug.
- **TdP**: the FDA-approved labeling includes mention of cases or a risk of Torsades de Pointes (TdP).
- **Cases in Lit**: there are case reports of TdP in the medical literature.
- **F>M (Females>Males)**: substantial evidence indicates a greater risk (usually a two-fold) of TdP in women.
- **Off Market**: this drug has been removed from the US market because of drug-induced TdP.

This list is maintained by Raymond L. Woosley, MD, PhD, Associate Dean for Clinical Research at Georgetown University (WoosleyR@Georgetown.edu). Suggested additions, deletions and references are most welcome; the list has benefited immensely from the input of practicing physicians and other researchers in the field. This page will be updated as new information becomes available. The content of this Table is for public use, free of charge and for information only. It is not intended to be used in any other manner. The author disclaims any liability, loss, injury, or damage incurred as a consequence, directly or indirectly, or the use and application of any of the contents of this Table. The information presented on this site is intended as general health information and as an educational tool. It is not intended as medical advice. Only a physician, pharmacist, or other health care professional should advise a patient on medical issues and should do so using a medical history and other factors identified and documented as part of the health professional/patient relationship. The entire content of this site is protected by International and United States of America copyright laws.
### Implications of ICH S7B study results (non-negative / positive)

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<tr>
<th>Conditions</th>
<th>hERG assay</th>
<th>and/or in vivo</th>
<th>Consequences</th>
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| Human therapeutic plasma concentration not known | Ratio of IC50 hERG / EC50 of primary pharmacological effect: 30 - 100 (non-negative) | In vivo QT assay shows < 10% QTc increase (negative) | 1) Proceed to nonclinical follow-up studies.  
2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies  
3) Routine monitoring of ECG in all subsequent clinical studies |
| Human therapeutic plasma concentration not known | Ratio of IC50 hERG / EC50 of primary pharmacological effect: 30 - 100 (non-negative) | In vivo QT assay shows ≥ 10% QTc increase (positive) | 1) Proceed to nonclinical follow-up studies.  
2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies  
3) Proceed to thorough QT/QTc study |
| Only estimate of human therapeutic plasma concentration known | Ratio of IC50 hERG / (estimated) free human plasma concentration: < 30 (positive) | In vivo QT assay shows $\geq 10\%$ QTc increase with high safety margin (positive). | Make go/no-go decision OR 1) Proceed to nonclinical follow-up studies. 2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies 3) Proceed to thorough QT/QTC study |
| Human therapeutic plasma concentration known | Ratio of IC50 hERG / free human plasma concentration: < 30 (positive) | In vivo QT assay shows $\geq 10\%$ QTc increase with low safety margin (positive). | Make go/no-go decision OR 1) Proceed to nonclinical follow-up studies 2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies 3) Robust monitoring of ECG in all subsequent clinical studies |
Conclusion

• Focus on electrophysiological parameters important and support risk evaluation
• But e.g. QT prolongation is one endpoint. Other CV risk factors need to be considered too, e.g. TRiAD = Triangulation, instability and Dispersion (Luc Hondeghem)
• Which QT prolongation is really predictive for TdP?
Conclusions

• S7B proposes a series of nonclinical tests believed to predict if a compound will prolong cardiac repolarisation *in vivo*, in animals and in humans.

• These data currently have different regional impact on the clinical development proposals contained in the E14 guideline.
Personal Recommendation

• Conduct preclinical studies early in development, describe issue!
• Methods are available and reliable
• Preclinical costs minor to clinical costs
• SP and QT studies expected from Agencies as EMA or MHW-Japan