Preclinical Perspectives of QT – Outlook from ICH Guidelines

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This abstract focuses on the essential preclinical investigations which can support the risk assessment of pharmaceutical compounds; the outlined strategies can facilitate the evaluation of the potential to prolong the QT-interval.

Safety Pharmacology Studies investigate the potential undesirable pharmacodynamic effects of chemicals or pharmaceutical compounds on vital organs or systems which are essential for sustaining life. The ICH Safety Expert Working Group has developed a hierarchy of organ systems with respect to their life-supporting functions. The most important functions are those of the cardiovascular, respiratory or central nervous systems. Drug-induced effects on these systems should be investigated prior to the first administration of substances to humans.

These 3 functions form the S7A Core Battery, which then can be complemented by Follow-up or Supplementary studies.

The ICH guideline S7A contains more general recommendations like timing of studies, compliance with Good Laboratory Principles or how to deal with metabolites etc. The ICH guideline S7B complements the requests for the cardiovascular functions and focuses on non-clinical studies for assessing the risk of repolarisation-associated ventricular tachyarrhythmia for human pharmaceuticals. The QT prolongation in the electro-cardiogram is considered to be the best biomarker for life threatening arrhythmias like Torsades de Pointes.

The current status of the guidelines is summarized in Table 1.

Table 1: Status of the International Conferences on Harmonisation of Guidelines for Safety Pharmacology (ICH /S/A+B)

<table>
<thead>
<tr>
<th>ICH No.</th>
<th>Title</th>
<th>CPMP Doc. No.</th>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>S7A</td>
<td>Safety Pharmacology Studies for Human Pharmaceuticals</td>
<td>CPMP/ICH/539/00</td>
<td>Step 5</td>
</tr>
<tr>
<td>S7B</td>
<td>Non-Clinical Studies for Assessing Risk of Repolarisation – Associated Ventricular Tachyarrhythmia for Human Pharmaceuticals</td>
<td>CPMP/ICH/423/02</td>
<td>Step 4</td>
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</tbody>
</table>

These two guidelines belong to the more recent ICH guidances. S7A was adopted by the regions of USA, Europe and Japan in 2000 and implemented in 2001 and the S7B reached step 4 in June 2005 and will be implemented in 2006. S7A informs in general about the requirements necessary for testing the vital functions usually in single dose studies in safety pharmacology. Table 2 summarizes the history of the safety pharmacology guideline.
Table 2: History of the safety pharmacology and ICH guideline development.

- 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

Overall, S7A differentiates three types of studies, i.e. core battery, follow-up and supplemental studies, and Table 3 details the functions which should be investigated predominantly.

Table 3: Core battery of tests under S7A.

- Investigate the effects of a test substance on vital functions:
  ➔ Central nervous system
  ➔ Cardiovascular system
  ➔ Respiratory system
  ➔ Other systems as appropriate
  ➔ Exclusion of a system or function should be justified

Table 4 illustrates which additional assays could be run to clarify issues derived from the core battery tests or other important information.

Table 4: Safety pharmacology studies carried out as necessary.

- Follow-up studies for Core Battery
  ➔ Provide a greater depth of understanding than, or additional knowledge to, that provided by the Core Battery (e.g. mechanistic studies)

- Supplemental studies

The purpose of supplemental tests is to evaluate effects of the test substance on systems not addressed by the core battery when there is cause for concern not addressed elsewhere (e.g. in toxicology).

S7 A expresses very clearly when such studies should be available and what conditions should be considered in regard to good laboratory procedures (Table 5)
Table 5: Timing of studies / ICH / S7A.

- Before first administration to humans:
  - Core Battery tests and follow-up/supplemental studies as appropriate
- During clinical development:
  - Additional studies as required, to clarify observed or suspected undesirable effects in animals or humans
- Before approval:
  - Effects on all organ systems, if not covered elsewhere (e.g. toxicology)

Table 6 gives clear directions when studies should comply with the principles of good laboratory practices,

Table 6: Application of GLP / S7A.

- Core Battery tests should be conducted according to GLP
- Follow-up and supplemental studies should be conducted according to GLP as far as possible
  - deviation should be justified and impact discussed
- Primary and secondary pharmacodynamic studies need not be conducted according to GLP

Among the vital functions in the core battery, special focus is given to the cardiovascular system (Table 7).

Table 7: 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
During the recent years an increase of regulatory concern about cardiovascular risk of new and available drugs is observed. Increasing awareness came up that non-cardioactive drugs, used sometimes for non-life-threatening diseases, can cause QT prolongation and serious dysrhythmias such as Torsades de Pointes (TdP). More and more compounds became known to be associated with QT prolongation and the potential to cause Torsades de Pointes. Table 8 provides a selection of such compounds.

Table 8: Drugs associated with prolonged QT and/or TdP.

| Amiodarone | Foscarin | Procainamide |
| Amtryptiline | Fosphenytoin | Quetiapine |
| Astemizole | Grepafloxacin | Quinidine |
| Bepridil | Halofantrine | Risperidone |
| Chlorpromazine | Haloperidol | Salmeterol |
| Cisapride | Ibutilide | Sertindole |
| Clarithromycin | Imipramine | Sotalol |
| Clemastine | Indapamide | Sparfloxacine |
| Desipramine | Isradipine | Tacrolimus |
| Disopyramide | Levomethadyl | Tizanidine |
| Dofetilide | Moexipril | Terfenadine |
| Doxepin | Moxifloxacine | Terodiline |
| Droperidol | Naratriptan | Thioridazine |
| Erythromycin | Nicardipine | Trimetoprim |
| Felbamate | Octreotide | Tamoxifen |
| Flecainide | Pentamidine | Terfaneadine |
| Fluoxetine | Pimozide | Zolmitriptan |

Accordingly, the ICH Expert Working Group of S7A was stimulated to continue their work, invite additional consultants and start to draft the new ICH guideline S7B, to address this specific concern. This guideline is entitled “ICH/S7B: Non-Clinical Studies for Assessing Risk of Repolarisation – Associated Ventricular Tachyarrhythmia for Human Pharmaceuticals” and the background of S7B is summarized in Table 9.

Table 9: Background of S7B guideline.
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).

The graphical sketch at bottom of Table 9 depicts ventricular tachycardia, extrassystoles followed by ventricular flutter.

To cope with this issue, a relatively flexible approach is given with the ICH/S/B non-clinical testing strategy as detailed in Figure 1.

![Figure 1: Non-clinical testing strategy for assessing the risk of repolarisation-associated ventricular tachyarrhythmia for human pharmaceuticals (ICH/S7B /Step 4).](image)

There are three basic parts of an essential package for testing the potential to cause QT prolongation of new compounds: the conduct of an in vitro test, usually the in vitro $I_{Kr}$ test, testing the Herg channel; then followed by an in vivo assay with high
quality electrocardiograms (ECGs) from relevant and predictive animals and thorough analyses of the QT interval. Then all existing knowledge and literature should be used to contribute to the first Integrated Risk Assessment. This assessment may result in a clear positivity for QT prolongation or there may be no indication for such a risk or the results do not allow a clear evaluation. In the latter case follow-up studies may be necessary, often action potential studies using different in vitro preparations or anesthetized animals. There may be also other relevant information from non-clinical or clinical studies. Accordingly, a number of subsequent Integrated Risk Assessments may be needed to allow a final statement on the evidence of risk of the new compound to prolong the QT interval when administered in humans. It needs to be stressed that the QT interval is a substitute for the risk one is really concerned about the Torsades de Pointes. Fortunately, these arrhythmias are rare, although they represent a sometimes serious discordance of the cardiac functions which can lead to sudden unexpected death.

In parallel with the development of S7B a clinical guideline (ICH/E14) was drafted and reached step 4 also in 2005. During the discussion between these two preclinical and clinical ICH Expert Groups the question was raised repeatedly, if toxicologists could exclude any risk for QT prolongation for humans with their testing strategies. Obviously, clinicians cannot exclude any such risk for future patient generations based on their clinical trial results only. In addition, the Food and Drug Administration (FDA) is comparing preclinical data based upon clinical results and seems to have identified few cases where QT prolongation was observed under clinical conditions while the preclinical tests were negative, but in none of these cases any report on Torsades de Pointes was received according to the FDA.

This discrepancy is the basis for the diplomatic text in regard to the need for availability of S/B QT studies (Table 10).

Table 10: Timing of S7B Non-clinical Studies / 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 term “should be considered“ opens all flexibility to do the studies before first time in humans or at a later stage of development. In practice, in most cases these studies are available before IND, because industry wants to cope with this issue in due time and wants to provide best safety to volunteers and patients. In addition, these studies can be done relatively easily today and can help to define concern or contribute to the selection of several candidates in parallel development.

In conclusion, however, it has to be stated that the S7B proposes a series of non-clinical tests which it is believed to predict the likelihood that a compound will prolong cardiac repolarization in vivo, in animals and in humans, but for some regions these data currently have little impact on the clinical development proposals contained in the draft E14 guideline. Data collection will continue by industry and regulatory agencies, the comparison of preclinical and clinical results should continue. The
evaluation of available preclinical assays will also continue and more refinement will be set into these studies and further new studies like those focussing on arrhythmic models may gain increasing importance.