FDA's Model-Based Strategies in the ICH-E14 Guidelines

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Regulatory Support for Model-Based Drug Development and Pharmacometrics

- 1994 Dose-Response
- 1998 Evidence of Clinical Effectiveness
- 1999 Population PK
- 2003 Exposure-Response
- 2009 EOP2a Meetings
- 2004 Critical Path Initiative
- 2012 Drug Interaction Guidance
- 2009 OCP Division of Pharmacometrics
Outline

- Brief history of drug-induced QT prolongation
- ICH E14 Guidance and the thorough QT study
- FDA experience with concentration-QTc modeling
Drug-Induced QT Interval Prolongation is Biomarker for Torsades de Pointes

HERG blockade by DRUG

Prolongation of action potential duration by HERG channel blocker

Prolongation of QT interval in ECG

ECG Indicating Torsades de Pointes

http://www.grt.kyushu-u.ac.jp/hergapdbase/
Drugs Withdrawn from Market as Result of QT Prolongation and/or Torsades de Pointes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of introduction</th>
<th>Therapeutic class</th>
<th>Year of withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenylamine</td>
<td>1960s</td>
<td>Antianginal</td>
<td>1988</td>
</tr>
<tr>
<td>Lidoflazine(^a)</td>
<td>1979</td>
<td>Antianginal</td>
<td>1989</td>
</tr>
<tr>
<td>Terodiline</td>
<td>1986</td>
<td>Antianginal/urinary incontinence</td>
<td>1991</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>1982</td>
<td>Antihistamine</td>
<td>1998</td>
</tr>
<tr>
<td>Sertindol(^b)</td>
<td>1996</td>
<td>Antipsychotic</td>
<td>1998</td>
</tr>
<tr>
<td>Astemizole</td>
<td>1986</td>
<td>Antihistamine</td>
<td>1999</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>1997</td>
<td>Antibiotic</td>
<td>1999</td>
</tr>
<tr>
<td>Cisapride</td>
<td>1988</td>
<td>Gastric prokinetic</td>
<td>2000</td>
</tr>
<tr>
<td>Droperidol</td>
<td>1960s</td>
<td>Tranquilizer/analgesic</td>
<td>2001</td>
</tr>
<tr>
<td>Levacetylmethadol</td>
<td>1997</td>
<td>Methadone substitution</td>
<td>2001</td>
</tr>
<tr>
<td>Dofetilide(^a)</td>
<td>1999</td>
<td>Class III drug for atrial fibrillation</td>
<td>2004</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>1958</td>
<td>Antipsychotic</td>
<td>2005</td>
</tr>
<tr>
<td>Clobutinol</td>
<td>1960s</td>
<td>Antitussive</td>
<td>2007</td>
</tr>
<tr>
<td>Dextropropoxyphene(^c)</td>
<td>1960s</td>
<td>Opioid analgesic</td>
<td>2009</td>
</tr>
</tbody>
</table>

\(^a\) Not commercialized; \(^b\) Re-introduced later following evaluation benefit-risk; \(^c\) In addition to QT-liability, safety in overdose was also an issue.

Terfenadine had Major Impact on Cardiac Safety of Drugs

**Mechanism**
- IKr blockade as mechanism for drug-induced QT prolongation and TdP

**Drug Interactions**
- Interaction of drugs can cause serious adverse events
- PK variability important for safety assessment

**Benefit-Risk**
- Small risk of drug-induced TdP outweighed the benefit of reduction of symptoms

Figure from Heist EK, Ruskin JN *Heart Rhythm, 2005; 2(11): S1-S8*
Two Regulatory Requirements: ICH E14 and S7B

Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

E14 Implementation Working Group
ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
Questions & Answers (R1)

Current version dated 5 April 2012

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Regulatory Guidelines are Keeping Torsadogenic Drugs Off the Market

Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System

Centerpiece of ICH E14: Thorough QT Study

• Determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation
  – Regulatory threshold is around 5 ms as evidenced by an upper bound of the 95% CI around the mean effect of 10 ms

• Randomized, blinded, positive- and placebo-controlled study in healthy subjects
  – Investigational drug is given at supra-therapeutic doses

• Guide intensity of ECG monitoring during drug development
  – QT prolonging drugs do not need TQT study
Statistical Analyses in TQT Study

- Measures of Central Tendency (primary analysis)
  - Largest time-matched mean difference between drug and placebo (baseline-adjusted) over collection period (especially at Cmax) < 10 ms

- Assay Sensitivity
  - Largest time-matched mean difference between moxifloxacin and placebo over 1-4 h window > 5 ms

- Categorical Analyses
  - QTc prolongation > 450 ms, > 480 ms, > 500 ms
  - Increase from baseline in QTc > 30 ms, > 60 ms

- Analysis of relationship between parent & metabolite concentrations and QTc changes
Positive TQT Study

$\Delta \Delta QTc \ (ms)$

10 ms

“Positive Study”

Mean and one-sided 95% CI
Clinical Considerations of “Positive” TQT Study

Does not mean the drug is proarrhythmic!

• More ECG data are need to assess proarrhythmic potential

Intensity of ECG monitoring will depend on:

• Magnitude
• Dose- and exposure-response
• PK properties of drug—Intrinsic and extrinsic factors that increase drug and metabolite concentrations
• Intended patient population with underlying increased proarrhythmic risk
• Adverse events than can increase proarrhythmic risk
• Other drug characteristics—safety pharmacology, toxicology, drug class, hysteresis
Concentration-QT Relationship is Essential for Positive Study

\[ \Delta\Delta Q_{Tc}, \text{ ms} \]

\[ \text{Concentration, } \mu\text{g/ml} \]

- **Therapeutic**
- **Supra-Therapeutic**
- **C\text{max}_{\text{Patients}}**
- **C\text{max}_{\text{Renally Impaired}}**
- **Drug Interaction**
Importance of Understanding the Concentration-QTc Relationship

- Better understanding of mechanism
  - Direct effect vs. indirect effect on QTc prolongation

- Dose selection for later clinical trials

- Doses or dosing regimens not evaluated in TQT study

- Dose-adjustments for patients with high drug concentrations due to concomitant medications, genetic polymorphisms and impaired organs of drug elimination
Examples Where C-QT Modeling had Impact on FDA Regulatory Decisions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anzemet (dolansetron)</strong></td>
<td>• Project the QTc prolongation in elderly and renally impaired patients in the product label.</td>
</tr>
<tr>
<td><strong>Zofran (ondansetron)</strong></td>
<td>• No single intravenous dose of ondansetron to exceed 16 mg due to the risk of QT prolongation.</td>
</tr>
<tr>
<td><strong>Celexa (citalopram)</strong></td>
<td>• Project the QTc prolongation at the 40-mg dose, which was not directly evaluated in the TQT study.</td>
</tr>
<tr>
<td><strong>Caprelsa (vandetanib)</strong></td>
<td>• Characterize QTc prolongation in the patients from ECGs obtained in phase 3 trials for the product label.</td>
</tr>
<tr>
<td><strong>Ranexa (ranolazine)</strong></td>
<td>• Characterize QTc prolongation in patients with highly variable pharmacokinetics.</td>
</tr>
<tr>
<td></td>
<td>• Project QTc prolongation in patients with hepatic impairment.</td>
</tr>
<tr>
<td><strong>Edurant (rilpivirine)</strong></td>
<td>• Supported no precautionary labeling statements for drug that prolongs QT at high doses</td>
</tr>
<tr>
<td><strong>Saphris (asenapine)</strong></td>
<td>• QTc prolongation (2-5 ms) is predicted by CEM and not the mean values reported from the IUT analysis (5-10.5 ms)</td>
</tr>
<tr>
<td><strong>Sertindole</strong></td>
<td>• Project QTc prolongation in patients who are CYP2D6 poor metabolizers for benefit-risk assessment.</td>
</tr>
</tbody>
</table>

FDA’s review of drugs is publicly available on website, [www.fda.gov](http://www.fda.gov)
Case: C-QTc Relationship Pivotal for Sertindole Regulatory Decision

- Antipsychotic for reducing risk of fatal and non-fatal suicide attempts in pts with schizophrenia
- Initial NDA received non-approval in late 90’s for QT prolongation, NDA re-submitted in 2008 following large safety study, SCoP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ΔQTcF, ms</th>
<th>ΔQTcF ≥ 60 ms</th>
<th>QTcF&gt;500 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(N=205)</td>
<td></td>
<td>(N=205)</td>
<td>(N=212)</td>
</tr>
<tr>
<td>Sertindole 20 mg/day</td>
<td>22</td>
<td>10.5%</td>
<td>1.9%</td>
</tr>
<tr>
<td>(N=210)</td>
<td></td>
<td>(N=210)</td>
<td>(N=212)</td>
</tr>
</tbody>
</table>

Pooled data from M93-113, M93-098, M92-762

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM248413.pdf
"Worst Case Scenario" for QTc Prolongation

- **ΔQTcF = 25 ms**
  - **Cmax ~80 ng/ml**
- **ΔQTcF = 40 ms**
  - **20 mg/day CYP2D6 PM or Inhibition**
- **20 mg/day CYP2D6 PM plus CYP3A4 Inhibitor**

Median ± 2*SE Quantiles
Mean (95% CI) Predicted

[Sertindole, ng/ml vs. QTcF, ms graph with annotations](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM248413.pdf)
Clinical Events Associated with QTc Prolongation

- Two observed cases of TdP in sertindole group
  - Clinical trials infrequently capture TdP, even with drugs known to have significant proarrhythmic effects
  - Few TdP events in a clinical trial do not provide reassurance of safety
- Imbalance in sudden cardiac death (SCoP)
  - 13 (sertindole) vs. 3 cases (risperidone)

PDAC, April 7, 2009
Has sertindole been shown to be acceptably safe for the treatment of schizophrenia? Yes-1; No-12

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM248413.pdf
Draft Regulatory Guidance on C-QTc Analysis

• Concentration-response analysis has established its utility in several settings
  • Informing dose selection for later studies
  • Providing insight into regimens not studied directly
  • Predicting the QTc effects of intrinsic and extrinsic factors that affect PK
  • Clarifying ambiguous results of a TQT study

• Use of concentration-response relationships in early phase studies to enhance evaluation of QT prolongation
  • Pooling QT and drug concentration data across doses, time, subjects, and studies can yield large data sets to which PK-PD models can be applied to predict concentrations at which QT prolongation could be clinically relevant.
Summary

- ICH E14 and S7B guidelines have been successful in keeping torsadogenic drugs off the market

- The TQT study is a clinical pharmacology study to assess whether a drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation

- Characterizing the relationship between drug concentrations and QT prolongation is important component for the overall assessment of QT liability