New Approach to assessing TdP risk without the thorough QT study

Regulatory Risk, uncertainty and implications

Krishna Prasad
MHRA
Disclaimer

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The references to the guidelines or papers from the above organisations, are factually represented.
E-14 and Thorough QT study: Achievements:

- **E-14 ( & S7B)**
  - provided a framework for evaluation of QT liability
  - Defined expectations (for sponsors)
  - Effectively reduced accidental discovery of QT liability of drugs

- **Thorough QT study**
  - Defined a set of parameters for identifying a risk
  - Provided the regulators and sponsors a decision making tool
  - Perhaps, standardised some of the interpretation and methods of testing

- **Disadvantages/ Criticisms---fact of life..**
Overall Risk & Benefit

• ~50% of drugs for oncology have QT liability

• the predictability of QT effect is variable (e.g. bosutinib)

• limited QT or torsadogenic risk is an expectation
There is Public Expectation...

Will regulators, industry, and the clinical community do a better job for patients next time?

"Drugs I can handle. It's reality that's lethal."

This is a perennial question.....
Pre-clinical evaluations

- hERG assay and in vivo studies (S7B)
  - Often the dossiers are non-compliant.
  - hERG trafficking – little information (Eg; Fluoxetine, Arsenic, petamidine and others)

- Repolarisation assays: (APD)
  - Limited information in most (APD_{90})
  - Evidence of EADs ?!

- Other indicators of proarrhythmias
  - TDR (transmural dispersion)-limited information

Overall predictability is variable.
Current paradigm; Models for prediction

Jonker et al 2005, CPT
Represents a model using **dofetilide** for an individual with baseline QT of 390 ms

Valentin JP, et al 2009 BJCP

- hERG based
- Relation to dosing and clinical doses needs clarity.
- Metabolite effects? – need better definition
Confounders for pre-clinical data

For in vitro studies

- Solubility and therefore concentration tested
- Adsorption to surfaces
- Test concentration limited by cytotoxic attributes
- Information on metabolites

In Vivo studies

- Data acquisition & analysis methods- (non-standard)
- Reproducibility of the systems
- Dose, interal and measurement points
- Interspecies differences
- Distinction of Multiple channel effects-
Regulatory risk

Current paradigm for prediction.

• is a hERG centric approach sufficient??!!

• Need standards for SP study end points translation ➔ to clinical studies

• Evidence of predictive value of SP studies not publicly available consistently.

• Prediction good for QT/QTc but appears dependent on effect size
New Paradigm

Needs ability to

Will require;

- Improved predictability and accuracy (sensitivity/specificity)
- Better relation to defining Torsade especially if TQT is not available
Potentials scenarios
(Admittedly rare)

- (-) NC tests, Phase-1 (+) –QT prolongation
- (+) non-clinical test; phase I –equivocal
- inconsistent NC studies.

However,
In these cases, default position would be to opt for intense monitoring in late phases.
What next?!

- **In Silico methods**
  - CR data from HTS
  - Medium throughput patch clamps
  - Multi parametric QSAR
  - AP simulation assay

- **Limitations**
  - Channel specific changes
  - Accuracy (Sn/Sp)
  - Variability (with HTS screening)

- **Stem cells**
  - Human cardiac myocytes
  - iPSC - CM
  - iPSCs
  - Undifferentiated hESC

- **Limitations**
  - Phenotypic consistency?
  - Ion channel expressions
  - Availability for HTS
  - Discrepancy between isolated rabbit hearts & hESC-CM cells in potency.
Summary

Current paradigm
- may not be sustainable
- Preclinical tests often non-standardised, and variable.
- Predictability for QT effect but not TdP.

A new paradigm
- or panel will need to address accuracy
- Unequivocal NC and Inconsistency with early phase studies will need to be tackled.
Back Up slides
Limitations of current paradigm (regulatory context)

- CV safety evaluation is an inescapable fact
- TQTs burdensome
  - Expense--- (\(\times 10^5\))
  - Time (delayed development programmes)
- Risk of TdP is elusive
  - QT liability defined but relation to TdP imprecise