CiPA- Regulatory considerations/ Next steps

K Prasad, MD, FRCP
Licensing Division, MHRA,
Cardiovascular WP of EMA
Challenges/ Regulatory considerations

1. “Construct” of the CiPA package
   • What and How different from S7B/ E-14 (?)

2. Cross-Validation - of the package including proposed cutoffs
   • Experience with different data sets..

3. Implementation of methodology..
   • Industry engagement and uptake for routine

4. Labelling & HCP Communication
   • Labelling
   • Enhance understanding
CiPA as a “package”

- What it does it include and are all components mandatory?
  - i.e., in silico, myocyte and clinical ECG

Need a decision tree

- Where applicable--- Discovery, Screening or further development?
- Sufficiently adaptive for internal as well as regulatory decision making
- Provides some flexibility of approach but largely standardised
- Ideally should avoid repetition of experiments e.g.,
When might CiPA assessment be useful?

- The biggest opportunity in early phase development lies in identifying risk from compounds that have poor channel selectivity (hERG) but have an important therapeutic potential.
  - hERG positive (narrow safety margin)
  - have effects on other channels – that may or may not be beneficial in all therapeutic contexts.
  - Prolong QTc in vivo animal studies

- Second, in defining risk of arrhythmia and providing a more comprehensive grading – and managing risk communication to health care professionals.
Sponsor uptake

Uptake by sponsors of CiPA and its advantages

Need prospective data to evaluate utility.

SPS survey 2017

56 % very familiar with S7B
~40% NOT familiar with E-14
61% incorporate Ion channel elements of currently
31% use stem cell approaches
21% (only) use in silico modelling parameters

Need to overcome some of the barriers
Some thoughts on Validation

• Robust testing method that is transferable to external laboratories/personnel

• Standardise protocols across different laboratories

• Experiments should conform to GLP standards for Regulatory purposes

• Have we studied enough compounds (variety) to gain comfort and confidence?

Some validation methods (e.g., ROC curves) could be very sensitive to errors in gold standard classifications.
CiPA: In Silico / ion channel model

- Opportunity for standardized protocols that can be adopted early in development
- Facilitates comparison of drug properties generating risk metrics and Perhaps aid regulators to compare drug potencies and therefore anticipate effects early
- Better translation of effects to human model.

But;
- The quality of ion channel data is critical.
- Experience from a wider sponsor group and sets of databases is needed.
- Need better understanding of effect of risk classification on other and subsequent studies.
CiPA: Myocyte component

- Offers advantage of routine testing of compounds with a ready supply of established cells using standardized parameters/methods.
- May obviate need for animal testing, selection of animal model and interspecies differences.
- Higher throughput than animal tissues based approaches.

However;
- Channel expression differences across cell lines,
- May underestimate effect on certain channels (limited reproducibility
- False negative findings that may arise from limited experience of certain technologies.
Difficult areas

• Risk classification- low / intermediate / high risk
  – Cut off values for risk stratification e.g., proximity of Low and intermediate risk (verapamil & chlorpromazine)
  – Discordance and false negatives ( e.g., Beperidil in myocyte /IPS-CM assays )
  – Limited predictivity for some channel effects in certain CiPA experiments ( e.g.- late Na & hIPSc-CM)
  – Difficulties with classification of Diltiazem

• For prospective evaluations, these do present an issue for sponsors and regulators
Clinical Phase & new BMs-- where to?

- J-T peak or QTc
  - Reproducibility & interpretation
  We need experience from different data sets to determine feasibility, reproducibility & applicability across wide range of compounds e.g. Dolasetron
  - Where does this fit with CR approaches?

Challenge is to obtain clarity of relative merits of ECG biomarkers & the advantages!

Can we develop the other parts of CiPA to limit the need for clinical phase ECGs?
True Challenge of a MIC blocker?

No reported TQT study.

How does CiPA identify such issues prospectively?

RESTORE SR; Heart Rhythm 2016;13:1777–1783

CONCLUSION Vanoxerine is an oral, mixed ion channel blocker with I_{Kr}, I_{Na}, and L-type calcium channel activity. While oral therapy with 400 mg of vanoxerine appears effective for the termination of recent onset AF/AFL, its use was associated with a significant risk of ventricular proarrhythmia in patients with SHD.
Decision trees

We should look for an integrated decision tree!
Next Steps:

1. Encourage (more) sponsors to share experiences
2. Cross validation (?!)
3. Relative positioning – including advantages
   - Integration with S7B/E14
4. Internal deliberations (Regulatory groups)
5. Presentation of data to ICH Discussion group (started)
6. Discussion at ICH IWG.
   - Update S7B/ E-14 or new multidisciplinary guidance?
Thank you for listening.

Krishna.Prasad@mhra.gov.uk