Lankenau Medical Center
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# CV Safety Assessment in Drug Development: Need for Individual Dedicated Studies vs. Monitoring Throughout Development and Risk Management

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# Disclosures

- Dr. Kowey has consulted for over 90 drug companies on an assortment of products.
- All of his work uses a fee-for-service arrangement at fair market value
- He holds no equity interest in any pharmaceutical company and his 401K and other retirement accounts are doing about as poorly as yours

# Non-Cardiac Drug Safety

- Low frequency events
- Public health issue because of volume of exposure
- May not be discoverable during routine clinical development
- May lead to market withdrawal with consequent public/media/political fallout

# CV safety has evolved into an area of prime concern in ALL of drug development because:

- Antecedent CV disease appears to increase the probability of adverse CV events
- CV disease is ubiquitous in many target populations (e.g. pulmonary and urogenital disease).
- Elder treatment targets (Alzheimer's and Parkinson drugs)
- Overlapping membrane/receptor MOA (e.g. antipsychotics and constipation drugs)

# Powerful Precedent: Cardiac Repolarization

- QT prolongation as a surrogate for a particular form of proarrhythmia: TdeP
- Now a required component of nearly every drug registration
- Guidance documents galore with instructions about methods of measurement, analyses, and data interpretation
- Grave labeling/approval implications

# Principal Mechanisms of Cardiac Harm

- Pro-arrhythmia
- Pro-thrombotic
- Pro-ischemic
- Hypertensive
- Hypotensive
- Valvulopathic
- Cardio-toxic/depressant

# Essential Issues

- How much CV harm can be anticipated from MOA, class, pre-clinical information?
- How much can we learn in selected populations under controlled circumstances?
- Are there reliable surrogates (HR, BP, QT, biomarkers)?
- What is the threshold for go/no go decisions based on CV hazard?

# Cardinal Principle

- In every case in which a cardiac safety issue is uncovered, the decision to proceed with development, regulatory submission, approval, or continued marketing must rest on the drug's benefit, specifically, the unmet need within a given therapeutic area.
- Examples: tetrabenazine, vandetanib, bedaquiline.

# Pre-Clinical Studies

- Required for many reasons and in some cases may assist in candidate selection
- Beyond HERG, little uniformity or agreement
- Some models (wedge, pacing-induced heart failure) may be helpful especially to sponsors in borderline cases
- Disappointing lack of validation or concordance (e.g. HERG and TQT).

# Dedicated Studies: Factors to Consider

- Subject safety
- Exposure time/concentration (metabolites)
- Target vulnerability
- Metric variability
- Response variability
- Cost/timing
- Margin for concern

# Specific Scenarios

- Dedicated study feasible for ECG/EP concerns but not possible for assessing direct myocardial toxicity
- Trial experience may be adequate if the signal size is expected to be large or there is a clear at risk sub-population that can be studied in context (CAD/CHF)

# Why labeling is NOT the answer

- Nobody reads them except announcers on DTC TV commercials
- They are used more as a weapon than an teaching tool by industry
- Instructions regarding CV monitoring are being delivered to an uninterested and uneducated audience

# REMS

- Little confidence in routine measures such as labeling, SAER, patient information packages
- Little proof that “ramped up REMS” (central pharmacy, limited distribution, physician registration) provides incremental value
- Fear that draconian measures like “no blood, no drug” will kill new drug uptake

# Post-Marketing Studies

- Not so simple and not quick
- Companies not rewarded for alacrity or punished for reticence
- Uncontrolled study results are impossible to decipher
- Salvation may be large electronic data sets like Sentinel (and we will be hearing more about that today)

# Can a CV safety signal be detected in the ordinary clinical trial context? It depends on:

1) Precedent
2) Signal size
3) Study size
4) Study population
5) Detection methods
6) Surrogate reliability
7) Generalizability
8) ***Benefit*** or its perception

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# Frank A. Clark

"If you find a path with no obstacles, it probably doesn't lead anywhere."