Adding Safety Pharm Endopoints To General Tox Studies - II

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Should Safety Pharmacology Cardiovascular Endpoints be exclusively collected from the General Toxicology Study?

- Although it is possible to include some Safety Pharmacology cardiovascular endpoints into standard Toxicology studies, it may not be optimal in some cases.
Regulatory Drivers

- **S7A**
  - “Safety pharmacology studies prior to the first administration in humans may not be needed for cytotoxic agents … However, for cytotoxic agents with novel mechanisms of action, there may be value in conducting safety pharmacology studies.”
  - “For biotechnology-derived products that achieve highly specific receptor targeting, it is often sufficient to evaluate safety pharmacology endpoints as a part of toxicology and/or pharmacodynamic studies; therefore, safety pharmacology studies can be reduced or eliminated for these products.”

- **S9**
  - “Conducting stand-alone safety pharmacology studies to support studies in patients with advanced cancer is not called for. In cases where specific concerns have been identified that could put patients at significant additional risks in clinical trials, appropriate safety pharmacology studies described in ICH S7A and/or S7B should be considered.”

- **S6**
  - “Safety pharmacology studies measure functional indices of potential toxicity. These functional indices may be investigated in separate studies or incorporated in the design of toxicity studies.”
Business Drivers

- Reduce Animal Use
  - Studies in telemetry equipped animals for biological or cytotoxic agents may limit the use of the animals for subsequent studies

- Reduce Cost
  - Incorporating endpoints into a single study can theoretically reduce overall development cost
Scientific Drivers

- Obtain CV data from Repeat Dose
- Determine effect of Cumulative Exposure
- Correlate with other data
  - Histopathology, Clinical Pathology, Bio-markers
### Precedent from Survey of Biologicals

******Safety Pharmacology (SP) Assessment of Biopharmaceuticals: A Survey of Past Practices.******

<table>
<thead>
<tr>
<th>Modality</th>
<th>BLAs</th>
<th>Dedicated SP</th>
<th>Integrated SP</th>
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<th>No Data</th>
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<td>Antibodies</td>
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<tr>
<td>Proteins/Peptides</td>
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<td>Enzymes</td>
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<tr>
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<td><strong>11</strong></td>
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<tr>
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<td><strong>12</strong></td>
<td><strong>33</strong></td>
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</table>

All BLA approval packages (FDA & Pharmapendium sites) from 1980-2011 were reviewed to record modality and type of SP study conducted.

SP= Safety Pharmacology

Integrated SP indicates that SP endpoints were evaluated in toxicity studies.

No SP indicates that no SP studies were performed.

No Data indicates that no pharmacology/toxicology reviews were found.
Risk: Impact on Data Quality

- Collecting ECGs is pretty straightforward, but:
  - Parallel study design means statistical sensitivity takes a hit
  - Snapshot at Cmax will tell a limited story
  - Collection process may cloud measurement
## Study Design Impacts on Power

<table>
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<th>QT</th>
<th>QTc</th>
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<td>26.9</td>
<td>16.0</td>
<td>27.8</td>
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</tbody>
</table>
Risk: May lose data due to Toxicity

- What you start out with may not be what you end up with
  - Regulatory studies with biopharmaceuticals or oncology products may have no pre-existing data to inform as to long term toleration
  - Treatment related toxicity may compromise animal health or even eliminate dose groups
    - This may complicate the interpretation of data
Risk: Data relevance to the concern?

- Not everything that counts can be counted and not everything can be counted counts.

- Likelihood of mAb interaction with hERG channel is very low
  - Collection of ECG data may be the least valuable of all the possible parameters
  - Unlikely to reveal other potential issues
Technology to the rescue

- JET collection can provide near telemetry quality data
- JET-BP may provide similar data quality and data density as for telemetry

But the parallel design is not as sensitive as a Latin Square Crossover design
  - What signal threshold are you comfortable with?
Best Strategy

- Determine if CV endpoints are critical to risk assessment
  - Target Liability Assessment
  - Class effect
  - Target tissue binding
- Design study to measure the appropriate endpoints
  - Repeat dose dedicated telemetry studies may be best