Summary of results from pre-workshop assignment: In vivo practices

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April 14, 2014
Outline

• Background on pre-workshop homework assignment

• Summary of in vivo results:
  – Why conduct an in vivo test?
  – Ideas to optimize the animal models

• Conclusions

Views expressed are those of the non-FDA pre-workshop participants.
Background on pre-workshop homework assignment

• Distributed on Nov. 7, 2013

• Solicit information on current practices for thrombogenicity testing

• Feedback was used to:
  – Inform agenda topics
  – Inform panel discussions

30 responders

- Industry 56% (17)
- Academic 30% (9)
- Test House 7% (2)
- Other 7% (2)
Why conduct in vivo thrombogenicity testing?

Q6b: For what reason do you conduct in vivo thrombogenicity?
   (22 responses)

- Contributes to preclinical safety assessment: 4 responses
- Satisfy regulatory guidance: 10 responses
- Both: 8 responses

Q13a: Is the 4hr unheparinized canine model clinically relevant?
   (24 responses)

- Yes: 4 responses
- No: 20 responses

Views expressed are those of the non-FDA pre-workshop participants.
How can we reduce in vivo variability and increase predictivity?

<table>
<thead>
<tr>
<th>Factor</th>
<th># of responses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use anticoagulant (if indicated)</td>
<td>5</td>
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<tr>
<td>Use longer duration (per indication)</td>
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<tr>
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<tr>
<td>Use clinically relevant vessel size</td>
<td>4</td>
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<tr>
<td>Use within-animal controls</td>
<td>4</td>
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<tr>
<td>Use arterial placement (if indicated)</td>
<td>2</td>
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<tr>
<td>Use fluoroscopy/ultrasound</td>
<td>2</td>
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<tr>
<td>Standardize fluid/ventilatory support</td>
<td>2</td>
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</tbody>
</table>

*Summary of feedback that received > 1 response

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Response demographics: device type

- Catheters: 21% (18)
- Stents: 14% (12)
- Bypass: 11% (9)
- Hemodialysis: 12% (10)
- Grafts: 14% (12)
- VADs: 12% (10)
- Other: 16% (13)

n=84
In vitro assessment strategies

Q1: In vitro Test Methods: Supporting US Regulatory Submission

Responses

<table>
<thead>
<tr>
<th>Type</th>
<th>Static (13)</th>
<th>Flow Loop (11)</th>
<th>Chandler Loop (2)</th>
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<td>Stents</td>
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<tr>
<td>Bypass</td>
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<tr>
<td>Hemodialysis</td>
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Q1: In vitro Test Methods: Developing materials for device use

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Q1: In vitro Test Methods: Supporting OUS Regulatory Submission

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In vitro methods:

**blood age, anticoagulant, source**

**Q4: Blood Age for Testing (24 responses)**

- < 1 hour: 9 responses
- 1 - 4 hours: 12 responses
- 4 - 24 hours: 3 responses
- > 24 hours: 0 responses

**Q4: Choice of anticoagulant (26 responses)**

- Heparin: 18 responses
- Sodium Citrate: 6 responses
- ACD: 2 responses
- None: 0 responses

**Q4: Blood Source (27 responses)**

- Human: 25 responses
- Rabbit: 10 responses
- Bovine: 8 responses
- Ovine: 6 responses
- Swine: 5 responses
- Canine: 4 responses
- Rodent: 3 responses
- Primate: 2 responses
Most common in vitro endpoints

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Correlation of in vitro tests/endpoints with clinical outcomes

Q11: Which in vitro tests best correlate with clinical outcomes? (10 responses)

- None: 4 responses
- Flow Loop: 2 responses
- Chandler Loop: 1 response

Q11: Which endpoints correlate with clinical outcomes? (14 responses)

- platelet adhesion (17)
- Platelet count (19)
- Microscopy (16)
- PTT (17)

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How can we reduce variability and increase predictivity?

Q5: Factors to optimize *in vitro* tests

- Use industry relevant controls: 6 responses
- Concentration of anticoag.: 4 responses
- Screen human donor blood: 3 responses
- Prompt handling: 2 responses
- Increase replicates: 2 responses

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Review

Most common in vitro testing strategy:

- **Design**: Static or Flow Loop
- **Blood**: Sourced from humans, anticoagulated with heparin or sodium citrate, and used for testing within 4 hrs
- **Endpoint**: PTT, microscopy, platelet count, and platelet adhesion
Summary of results from pre-workshop assignment: Device specific considerations

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Regulatory test strategy stratified by device type

Q10: Test strategy based on type of modification - experimental

- Brand New Device
- Material Change
- Design/Geometry Change

Q10: Test strategy based on type of modification - justification

Device specific considerations

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Most common *in vivo* endpoints

Device specific considerations

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In vivo model system: device type

6a: In vivo Test System: Catheters

6a: In vivo Test System: Stents

6a: In vivo Test System: Grafts

Views expressed are those of the non-FDA pre-workshop participants.
In vivo model system: device type

6a: In vivo Test System: Bypass

Responses

Rodent (1) Rabbit (7) Canine (13) Swine (16) Ovine (14) Bovine (4) Primate (1)

Non-Anticoagulated  Anticoagulated

6a: In vivo Test System: Hemodialysis

Responses

Rodent (1) Rabbit (7) Canine (13) Swine (16) Ovine (14) Bovine (4) Primate (1)

Non-Anticoagulated  Anticoagulated

6a: In vivo Test System: VADs

Responses

Rodent (1) Rabbit (7) Canine (13) Swine (16) Ovine (14) Bovine (4) Primate (1)

Non-Anticoagulated  Anticoagulated

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What is the most clinically relevant in vivo system to evaluate thrombogenicity?

Model based on size and intended anticoag.

- Ovine: 6 responses
- Porcine: 6 responses
- Canine: 2 responses
- Rabbit: 2 responses
- Bovine: 2 responses
- Goat: 1 response

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Conclusions

• Common in vivo endpoints included thrombus surface area, distribution, and weight; vessel patency; and gross pathology
  – Was not markedly different across devices

• Brand new device or material change most likely to result in thrombogenicity testing
  – Justification for omission of testing common for changes in device geometry

• Anticoagulation used in most device evaluation (exception of hemodialysis and catheters)

• Ovine and porcine were cited as most clinically relevant test species

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