

FDA Public Workshop: Methods for Thrombogenicity Testing of Medical Devices

April 14, 2014, FDA White Oak Campus, Building 31 Great Room B/C

Panel I – Discussion Questions:

1. Given the complexity of the coagulation process, a battery of *in vitro* tests instead of a single *in vitro* test may be needed to understand whether a material is likely to be thrombogenic in a patient. Based on the homework assignment responses, platelet adhesion, platelet count, microscopy, TAT and PTT are commonly used.
 - a. Which of these tests would be most appropriate to include in an *in vitro* test battery to provide a sufficiently complete understanding of thrombogenic potential for (1) materials, and (2) for dynamic testing of devices, and why?
 - b. Are there any additional *in vitro* tests that may be important to support regulatory decisions? For example, should FDA also request tests to demonstrate that materials are not fibrinolytic; i.e. both thrombogenic and fibrinolytic tests? Why or why not?
 - c. If a dynamic *in vitro* test were developed to assess geometry-mediated thrombogenicity of devices such as catheters or stent delivery systems, what are important considerations for the development of such a test?
2. It's important to understand the potential impact of blood source, blood age, anticoagulation, and use of control materials on the predictive nature of different *in vitro* tests. Therefore, please discuss the following:
 - a. A majority of respondents indicated that they used human blood, about 1/3 reported using rabbit blood, and some used bovine and ovine blood.
 - i. Are there particular *in vitro* (1) material tests, and (2) dynamic tests where only human blood should be used?
 - ii. Which *in vitro* tests can be conducted using blood from non-human species, and how does the data compare across the species?
 - iii. Have you investigated the differences in coagulation and fibrinolytic properties of different species and how choice of species might impact the findings of particular *in vitro* tests? If yes, can you provide examples of choosing a particular species because of their coagulation profile?
 - b. A majority of respondents indicated that blood for *in vitro* testing was used within 4 hours of draw, with about 50% using the blood within 1 hour. Prompt handling of blood was also identified as an important consideration to reduce variability in test outcomes.
 - i. Please discuss how blood age can influence the results for various *in vitro* tests.

- ii. Is there a timeframe after which *in vitro* (1) material test, and (2) dynamic test results begin to be less clinically predictive?
 - iii. Are there recommendations for storage of blood prior to testing; i.e. anti-coagulant and room temperature vs. refrigeration vs. freezing, etc.?
 - c. The concentration of anticoagulant was identified as a primary factor contributing to variability and impacting predictivity of *in vitro* testing. For example, if the level of anticoagulation is too high, it could mask the ability to detect a positive response. Alternately, if the level of anticoagulation is too low, clotting unrelated to the device material or geometry could result.
 - i. Discuss how validation testing or initial test set-ups could include bracketing the concentration of anticoagulant using a “step-up” and/or “step-down” process until the concentration is optimized to allow for detection of positive responses without spurious clotting.
 - ii. How might one determine the acceptable baseline coagulability of the blood in vitro?
 - iii. Are there certain *in vitro* (1) material tests, and (2) dynamic tests where it is more appropriate to use one anticoagulant over another?
 - iv. If anticoagulants (e.g., sodium citrate or ACD) are being formulated in house, what quality control measures should be in place to ensure consistency in the final product?
 - d. The use of controls was identified as the single most important factor for optimization of *in vitro* testing to confirm that the study is valid and to assist with data interpretation. What positive, negative, and/or comparative device controls are useful for various *in vitro* tests? How should these controls be validated?
3. Variability has been identified as a limitation to the current in vivo 4 hour non-anticoagulated venous implant (NAVI) canine thrombogenicity study design. Discuss how the following could be modified to optimize the test:
 - a. Use of anticoagulant;
 - b. Use of clinically indicated indwelling time (worst case?);
 - c. Use of clinically relevant vessel size;
 - d. Use of clinically indicated arterial/venous placement;
 - e. Use of fluoroscopy/ultrasound for device placement;
 - f. Use of standardized fluid/ventilatory support;
 - g. Use of a standardized scoring system across laboratories

Panel II – Discussion Questions:

BACKGROUND: For short-term and long-term use devices, with large and small surface areas, it isn't always clear what pre-clinical *in vitro* and *in vivo* thrombogenicity tests are sufficient to evaluate safety.

4. For short term use devices such as guidewires; ablation, balloon and mapping catheters; and stent delivery systems, the 4 hour NAVI canine study is commonly requested, especially if other large animal testing is not available for the device. Discuss alternative strategies to provide reasonable assurance that *in vivo* thrombogenicity of the device is not likely to be a concern. For example, discuss whether a combination of some/all of the following might be sufficient for a material change versus a change in geometry versus to support an entirely new design:
 - a. A battery of *in vitro* tests for material thrombogenicity (e.g., PTT, TAT, ?);
 - b. A dynamic *in vitro* test to assess geometry-mediated thrombogenicity;
 - c. Dimensional engineering drawings;
 - d. Surface analysis (e.g., 40X magnification) to confirm smoothness of surfaces, and minimal gaps/junctions between components;
 - e. Manufacturing release "Final Inspection" assessments; and/or
 - f. Information from relevant preclinical animal or clinical use within the United States (US) or outside the US (OUS), if any.
5. For indwelling catheters such as central venous catheters, we usually request data from long-term animal studies (relevant to the indicated use time which is usually 30 days) to evaluate thrombogenicity-associated endpoints. In some cases, manufacturers will instead provide results from 4 hour NAVI canine studies or 8 hour close loop *in vitro* dynamic studies, but the use of this information as a basis for regulatory decisions is limited by our understanding of the clinical predictivity of these approaches. Please discuss which types of thrombogenicity evaluations might be most relevant for this device type.
6. Patients receiving hemodialysis treatment are exposed to the ultrafilter of conventional and high permeability hemodialyzers and the hemodialysis blood tubing sets multiple times each week, with a single in-center treatment lasting up to 4 hours. Some patients receive hemodialysis at home for up to 12 hours/day. In addition, patients may receive hemodialysis treatments for years. For these devices, assessment of chemical and mechanical hemolysis is important. Thrombosis is a safety concern, especially when new materials or major material changes are applied to the ultrafilter or blood tubing set. The following questions are pertinent to thrombosis testing for hemodialyzer and blood tubing sets:
 - a. Because the hemodialyzer ultrafilter and blood tubing components serve as conduits for blood, and are not inserted directly into a vessel, please discuss the clinical predictivity of *in vivo* implant models for these components. For pre-clinical and clinical studies, which *in vivo* endpoints (e.g., activated clotting time, PTT) are useful to monitor coagulation status?

- b. In a clinical setting, how does the type of anticoagulant (e.g., heparin *versus* citrate) influence the choice of endpoints to assess thrombogenicity?
 - c. Could a battery of only *in vitro* tests, including an assessment of thrombosis, coagulation, platelet, and complement activation be sufficient to evaluate thrombogenicity of ultrafilters and tubing sets? If so, please discuss which particular *in vitro* test(s) could be used to address thrombogenicity of the ultrafilter and blood tubing.
7. Hemodialysis catheters can be implanted acutely (up to 30 days) or chronically (months to years, if patency can be maintained). For long-term (chronic) hemodialysis catheters, large animal safety studies are usually conducted to support the chronic indications. However, there is more variability in the types of assessments conducted to address the thrombogenicity potential of acute hemodialysis catheters. In some cases, manufacturers will provide results from 4 hour NAVI canine studies, large animal safety studies (duration varies, >4 hours), or various *in vitro* static or dynamic tests. The use of these different methods as a basis for regulatory decisions is limited by our understanding of the clinical predictivity of these approaches.

Please discuss whether the 4-hour NAVI canine study adequately addresses thrombosis concern associated with an acute hemodialysis catheter that may have an indwelling duration of up to 30 days. As a part of your discussion, please also address the following:

- a. What *in vitro* and/or *in vivo* tests are appropriate to address the thrombosis concern with the acute hemodialysis catheters that may indwell up to 30 days?
 - b. What *in vitro* and/or *in vivo* tests are appropriate to address the thrombosis concern with the chronic hemodialysis catheters?
 - c. What nonclinical (animal) tests can replace *in vitro* tests for acute and chronic hemodialysis catheters?
8. For ventricular assist devices, we usually request data from long-term animal studies to evaluate thrombogenicity-associated endpoints. In addition, manufacturers will often provide data from PTT testing and computational fluid dynamic (CFD) studies in their applications, but use of this information to make regulatory decisions is limited by our understanding of the clinical predictivity for these approaches. Discuss whether there are any useful *in vitro* tests that can predict thrombosis in these devices.
9. For stents, and endovascularly-deployed and surgically implanted grafts, we usually request data from long-term animal studies to evaluate thrombogenicity-associated endpoints. In some cases, manufacturers will instead provide results from Chandler loop testing, but the use of this information as a basis for regulatory decisions is limited by our understanding of the clinical predictivity of this approach. Please discuss the benefits of this model for evaluating thrombogenicity of stents and/or grafts. How do you suggest standardizing/validating this model?

10. For cardiopulmonary bypass oxygenators and arterial filters, we request that hemolysis and blood cell depletion (as a function of blood cell count change) be investigated using a 6 hour in vitro circulation of blood through these devices, with results being compared to data from similar predicate devices. Blood component (platelet) functionality assessments are also requested for devices with new technology, materials or surface characteristics. Please discuss whether this testing approach is sufficient and when additional in vitro assessments for platelet activation markers (e.g., platelet factor 4), or coagulation activation markers (e.g., TAT) might also be important for evaluating device safety.