Welcome and Overview of the Current FDA Approach to Thrombogenicity Evaluation

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Methods for Thrombogenicity Testing of Medical Devices

Workshop Organizing Committee:

Program Committee:

- Kenneth Cavanaugh, PhD[b] (kenneth.cavanaugh@fda.hhs.gov)
- Rakhi Dalal, PhD
- Judy Davis, DVM
- Tanya Farooque, PhD
- Xin Fu, PhD, DABT
- Jennifer Goode[b] (jennifer.goode@fda.hhs.gov)
- Molly Ghosh, PhD, DABT
- Victoria Hampshire, VMD
- Michael John, MS
- Anchal Kaushiva, MS[a]
- James Kleinedler, PhD[a,b] (james.kleinedler@fda.hhs.gov)

Program Committee (cont):

- Qijin Lu, PhD
- Richard Malinauskas, PhD
- Karen Manhart-Byrnes, VMD, ANP, DACVP
- Steven Wood, PhD

Logistics:

- Susan Monahan
- Joyce Raines
- Anchal Kaushiva
- Jim Kleinedler

Special thanks to Erica Takai and Donna Lochner

[a]meeting coordinators [b]moderators

Workshop Logistics:

Format:

- Presentations (scientific presentations & homework survey results)
- Moderated discussion with lead discussants
  - Limited audience participation as time permits
  - Strict time limits for discussions

Ground Rules:

- Tent cards upright to comment
- State your name each time before you comment

Other:

- Box lunches, snacks and drinks are available for purchase in the lobby
- Visitors can only access Building 31 (workshop site)

Clinical concerns - Thrombogenicity:

- Thrombosis deposition: can lead to device malfunction.
- Thromboembolism: can lead to severe adverse events such as ischemic stroke, myocardial infarction or pulmonary embolism.
- Bleeding: (due to increased anticoagulation and/or antiplatelet therapy) can lead to hemorrhagic stroke.

Preclinical thrombogenicity assessments prior to human use:

- FDA relies on *in vivo* studies for many:
  - Implant devices where thrombogenicity evaluations are included in anticoagulated large animal studies which are conducted to assess safety and possible effectiveness

Preclinical thrombogenicity assessments prior to human use (cont.):

- FDA relies on *in vivo* studies for many:
  - Catheter-based devices (minutes to hours) where a 4-hour canine non-anticoagulated venous implant (NAVI) model* is often requested to assess potential for material-mediated and geometry-mediated thrombus formation.
  - Indwelling catheters (long-term/repeat use) where thrombogenicity evaluations are included in anticoagulated *in vivo* studies.

*validity of model and interpretability of data are often questioned

Device-specific thrombogenicity evaluations:

- Catheters:
  - Interventional catheters (10min-several hours): 4 hour canine NAVI study
  - Indwelling catheters (multi-day use): 30 day anticoagulated animal study with platelet activation and leukocyte information
- Stents/Grafts:
  - Thrombogenicity assessments included in anticoagulated large animal studies

Device-specific thrombogenicity evaluations:

- Ventricular Assist Devices:
  - Thrombogenicity assessments included in anticoagulated large animal studies
- Bypass circuit components:
  - CPBP: mechanical hemolysis, panel of *in vitro* coagulation assays
  - Hemodialysis/hemoperfusion: mechanical hemolysis, panel of *in vitro* coagulation assays (new materials: clinical thrombus assessments and complement activation)

Where the 4 hr canine NAVI study has been informative:

NAVI = non-anticoagulated venous implant

- Catheter geometries that can result in niduses for thrombus formation:
  - Gaps between shaft/balloon/markers;
  - Side port holes;
  - Stent securement components.
- Relative effectiveness of coatings designed to improve “hemocompatibility”
- Problems with molds that result in non-smooth surfaces

Concerns w/4 hr canine NAVI study:

NAVI = non-anticoagulated venous implant

- Clinical relevance of:
  - Canine implant model
  - Venous implant location: Worst case? (use in both venous and arterial vessels)
  - Unheparinized animals: Worst case? (use in both heparinized and unheparinized patients)
  - 4hour assessment (device use time and time-dependent nature of thrombus generation and resolution)
  - Impact of vessel:device diameter ratio on study findings
  - Impact of surgical technique on study findings
  - Nonstandardized scales (thrombosis) used across test labs
- How to assess clinical relevance of adverse study findings?

Workshop Objectives:

- Discuss the advantages, limitations and potential for optimization of *in vitro* and *in vivo* thrombogenicity tests used for regulatory submissions.
- Discuss strategies to optimize the design of a short term *in vivo* thrombogenicity model.
- Identify alternative *in vitro* data that can provide equivalent or improved insight into the potential for clinical thrombogenicity while minimizing expenses and animal use.

Workshop topics will include:

1. Strengths, weaknesses, and optimization of *in vivo* thrombogenicity test methods;
2. Current methodologies for conducting *in vitro* thrombogenicity testing (e.g., blood conditions, static versus dynamic methods, and different test endpoints);
3. Correlation between *in vitro/in vivo* thrombogenicity test results and clinical outcomes;
4. Special testing considerations for catheters, stents, grafts, ventricular assist devices, and bypass circuit components

Considerations for discussion:

- How might the following impact data expectations for FDA clinical trial or marketing submissions:
  - New materials or geometry of final device
  - Material changes after marketing
  - Geometry changes after marketing
- How should time-dependent factors be implemented in dynamic studies (*in vitro/in vivo)?*
- What research and/or methods standardization are needed to improve regulatory assessments?