Welcome and Overview of the Current FDA Approach to Thrombogenicity Evaluation

Jennifer Goode, BS, Biomedical Engineer
FDA Office of Device Evaluation
Division of Cardiovascular Devices

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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 \textit{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 \textit{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)
  – 4 hour 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?