FDA Questions to Panel

1. What is an appropriate method to characterize effectiveness or clinical improvement?
   a. Absence of AF? Please define absence of AF – symptomatic only or all AF. Please define the manner in which it can be measured.
   b. Reduction of AF burden? Please define AF burden and how it can be measured both pre- and post-treatment.
   c. A composite functional endpoint (e.g. hospitalization, cardioversion, days of work missed, etc.)? How is bias accounted for if investigators or subjects are not blinded to their treatment as in the traditional trial design?

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2. What trial designs are viable options to develop valid scientific evidence of the safety and effectiveness of a new ablation catheter system? Please consider the two example trial designs presented by FDA.
   a. What is the appropriate control for the study of the safety and effectiveness of ablation catheters for the indication of treatment of atrial fibrillation? Do the different types (i.e. PAF vs permanent AF) need different control groups?
   b. For what duration should safety of the ablation device be measured?
   c. For what duration should effectiveness of the ablation device be measured?

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- 3. Given that catheter ablation is an invasive therapy, if the control group is noninvasive medical therapy, what should the comparisons be for safety and effectiveness?

4. If a performance goal derived from the medical literature is used for either safety or effectiveness comparisons, what should the values be and why?

5. Based upon the discussion of trial design for percutaneous catheters, please discuss your recommendations for trial designs to study surgical ablation in a sole-therapy situation.

6. Please address the following issues with respect to anticoagulation:
   a. FDA agrees with the ACC guidelines which state "Drugs and ablation are effective for both rate and rhythm control, and in special circumstances surgery may be the preferred option. Regardless of the approach, the need for anticoagulation is based on stroke risk and not on whether sinus rhythm is maintained." Please comment.
   b. What data are needed to support instructions to discontinue anticoagulation after atrial fibrillation ablation?

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7. If trial endpoints focus on symptomatic recurrence, how important is it to capture asymptomatic AF recurrences? What are the implications of asymptomatic AF recurrences in terms of the long-term risks of AF (e.g. tachycardia-mediated cardiomyopathy) and, for example, the need for anti-coagulation?

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8. FDA currently classifies patients with AF into three groups: paroxysmal, persistent and permanent (according to criteria proposed in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation).
   a. Do you believe that different types of AF should be studied separately?
   b. Should there be differences in the definitions of effectiveness for each patient group following ablation therapy, and should they be followed differently? If so, please provide recommendations (for example, with respect to duration, type of monitoring)?

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9. What is the clinical implication of subjects undergoing ablation changing from permanent or persistent atrial fibrillation to paroxysmal atrial fibrillation? Should this impact the clinical trial design?

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10. Should atrial fibrillation ablation trials specifically study high risk patients (such as those with heart failure)?
   a. If the panel does not feel that specific (potentially high risk) patient populations should be included in the clinical trials, can trial results using restricted enrollment criteria be applied to the general population?
   b. If yes, are there specific groups to which such results should not be applied (such as patients with advanced heart failure, severe left ventricular systolic dysfunction or "giant" left atria)? How should such patient groups be handled in terms of device indications, warnings/precautions, etc.?

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11. Is it useful and/or important to collect information concerning atrial transport?
   a. If so, is there a specific method that should be used?
   b. What comparison should be used?

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