

DRAFT FDA Questions to the Panel
Circulatory Devices Panel Meeting
Alsius CoolGard 3000 System
March 17, 2005

Alsius is requesting to add the following new indication for use (IFU) to the CoolGard 3000 System:

“For use in the induction, maintenance and reversal of mild hypothermia in the treatment of unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation.”

In support of this request, the sponsor has submitted clinical data with their specific device from two different sources:

- A 13-patient prospective uncontrolled U.S. feasibility study and
 - A prospective, non-randomized, single-site observational registry with “matched” controls (AKH Registry Data).
1. Please discuss whether you believe the data provides reasonable assurance of safety for the proposed indication. In your discussion, please specifically address whether:
 - a. The manner in which the data was collected (prospective registry) provides adequate assurance that the rates of adverse events noted in the submission are representative of what might be expected in actual clinical practice.
 - b. The data adequately address the risks and potential concerns of intravascular cooling mentioned at the September, 2004 Panel Meeting, including bleeding, clotting, DIC, and ventricular fibrillation.
 - c. The increased rates of early pancreatic and renal injury raise any new or specific concerns.
 2. Please discuss whether you believe the data provides reasonable assurance of effectiveness for the proposed indication. In your discussion, please specifically comment on whether the issue of non-randomized data was adequately addressed by the propensity analysis.

3. Taking into account all pertinent clinical information available as well as your responses to the above questions, please comment on whether you believe the data provides an overall risk/benefit ratio which supports marketing clearance of the device in the United States for the proposed indication.

4. If you believe that the data currently submitted ***is*** adequate and sufficient to support marketing clearance:
 - a. Please comment on what specific elements should be included in the labeling to accurately reflect the risks, benefits, and proper use of the device including any modifications to the proposed:
 - i. indications for use statement (IFU),
 - ii. contraindications,
 - iii. warnings/precautions, and
 - iv. instructions for use.

For the latter, please comment on what specific rates of cooling, duration of cooling, optimal target temperature(s), rewarming rates, and optimal time to initiation of therapy are supported by the data or whether the general treatment guidelines proposed by the sponsor (32-34°C for 12-24 hours) are sufficient for labeling purposes.

- b. Please comment on whether you believe a post-market study should be required and if so, what the critical components and design of that study should be.

5. If you do ***not*** believe that the data presented today met the threshold for marketing clearance, please discuss what additional type and amount of clinical data would be required to meet this level of assurance. In your discussion please comment on:
 - a. The appropriate endpoints (including assessment scales and timing of assessments) which should be used to evaluate the effectiveness of endovascular cooling catheters for this indication.

 - b. Whether a randomized controlled trial (RCT) would specifically be required and if so, what the appropriate control group(s) would be. If not, please comment on what other types of trial design would be adequate.

 - c. Whether, due to the potential differences in standard of care between the international community and the United States, data collected in the U.S. would be required.