



American Society of Transplant Surgeons

February 29, 2016

Jeffrey E. Shuren, MD, JD
Director, Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Rm. 5456
Silver Spring, MD 20993-0002

Re: FDA-2015-N-1021 - Medical Device User Fee and Modernization Act; Notice to Public of Web Site Location of Fiscal Year 2016 Proposed Guidance Development

Dear Dr. Shuren,

The American Society of Transplant Surgeons (ASTS) appreciates the opportunity to comment on the Center for Devices and Radiological Health (CDRH or the Center) Guidance Development Initiative on Utilizing Animal Studies To Evaluate the Safety of Organ Preservation Devices and Solutions. ASTS is a medical specialty society representing approximately 1,800 professionals dedicated to excellence in transplantation surgery. Our mission is to advance the art and science of transplant surgery through leadership, advocacy, education, and training.

As the FDA notes in its solicitation of comments, the need for innovative solutions to the scarcity of viable transplantable organs is dire. Research in this arena is dependent upon the availability of safe and reliable animal models to assess post-reperfusion injury, and we applaud FDA's efforts to develop guidance for utilizing both in vivo and ex vivo animal models to evaluate emerging organ preservation technologies.

The FDA notice solicits comments on a number of specific questions, which are addressed below.

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(1) What are the potential limitations of an ex vivo model in assessing reperfusion injury, and how can these limitations be mitigated? In addition to markers for cell injury and function, histology, and the use of allogeneic blood during reperfusion, what measures can be taken to improve the data generated in an ex vivo model?

Landmark in vivo animal transplant experiments by Friend and colleagues (1) have demonstrated the validity of transplant simulated models and their ability to predict clinical feasibility (2). However, due to the complexity and interrelationships of factors that may result in ischemia reperfusion injury (IRI), the simulated reperfusion model, which typically involves an isolated system including only one organ and a perfusion solution, potentially underestimates the real overall injury that would be observed in human transplantation. A number of measures may be considered to improve the data generated using an ex vivo model.

First, in order to mitigate the limitations of the ex vivo simulation to assess ischemia reperfusion model, the model can be used as a means to test the relative impact of different preservation protocols (for example when compared to static cold storage) rather than as a surrogate to determine the absolute effects of ischemia and reperfusion injury on the organ. Under such protocols, the SCS group could function as a reference point against which new protocols can be tested.

Second, to further improve the data generated in an ex vivo model of simulated transplant reperfusion, any effort should be made to use whole blood (ideally from third party animal blood donors). This would more closely replicate the events that take place after reperfusion in a human transplant model, where the reperfusion occurs with blood that has a different immunological background than the organ. Under this premise, physiologic parameters of the allograft and biomarkers in the perfusate may be used as surrogate markers of allograft function.

Third, when preclinical ex vivo data is transitioned into human trials, simulated reperfusion of discarded human organs should be encouraged.

Finally, while improving the protocols and processes used in ex vivo animal models is important, it is at least as important for the research to be conducted by experienced teams with proven track records and peer-reviewed publications in the field.

(2) In an in vivo model, what are strategies to limit confounding factors, such as immunological responses and hemodynamic instability, from affecting the assessment of device-related reperfusion injury?

Due to the significant number of confounding factors that may affect the assessment of device-related reperfusion injury using an in vivo model, we recommend that in vivo transplant studies be mandated only for those technological innovations that are truly path-breaking and only for those perfusion solutions that include components that have never been tested in an in vivo model or in humans. Confounding factors may include not only immunological bias and hemodynamic instability, but also anatomical and pathophysiological differences among donor animals. Moreover, large animal transplants are technically complex; post-operative management is difficult; and highly specialized and dedicated facilities are necessary. Standardization of experimental design and reproducibility of results are extremely difficult to achieve in light of the multiplicity, complexity and interrelationships among the various confounding variables.

(3) Is there a perceived hierarchy of evidence regarding data obtained from an ex vivo model and those obtained from an in vivo model? Or rather, is it more judicious to view the two models as complements of each other?

Each of the two models entails different advantages and disadvantages. For this reason, they should be viewed as complements of each other.

(4) What role does the risk of the device play in the utilization of in vivo and ex vivo models? Regarding specific experimental parameters (e.g., length of preservation, total ischemic time), under what circumstances is it appropriate to test the worst-case scenario?

The worst-case scenario should be tested as much as possible using preclinical models. Length of preservation and total ischemic time both can and should be tested using the ex vivo simulated reperfusion model.

(5) What are the organ-specific challenges in developing in vivo and ex vivo models to assess reperfusion injury?

IRI primarily affects organ microcirculation, and each organ has a different microcirculatory environment and a different tolerance to organ reperfusion injury (including the resulting cell death and edema). For example, because a liver capsule can expand freely and has a high tolerance to edema and congestion, it may tolerate the edema following a bad ischemia reperfusion event in a manner that is different from a kidney or a composite tissue such as a limb (both of which have relatively poor tolerance to edema). IRI in lung transplantation is well defined and accepted by the community, whereas in heart transplantation its definition is not universally accepted and the real incidence is not known.

(6) What approaches would improve the in vivo and ex vivo study designs to ensure the generation of sufficient, meaningful data while limiting the number of animals used in such studies?

The number of animals used in these studies may be limited by using ex vivo simulated perfusion studies rather than in vivo studies, whenever possible.

We urge the FDA to proceed with this guideline development process expeditiously. In this regard, we note that the field of ex-vivo heart and lung perfusion of human organs has advanced quite rapidly in the past five years. In reference to heart ex vivo perfusion, a Phase III pivotal clinical trial was published in *Lancet* in April of 2015. This trial showed that standard human hearts can be preserved in a beating state with similar outcomes as cold static preservation, but with a significantly shorter ischemia time. A trial to use ex vivo heart perfusion in non-standard hearts is currently underway in United States. (EXPAND-Heart). In reference to ex vivo lung perfusion, one platform is approved by FDA for HDE (XVivo). Another platform (OCS) just completed a 340 patient study (INSPIRE trial) that will be presented in part at the upcoming ISHLT meeting. We are pleased at the progress of technological innovation and look forward to working with the FDA to expedite this critical research. If we can be of further assistance, please contact ASTS Executive Director, Kim Gifford, at kim.gifford@asts.org or 703-414-7870.

Sincerely,

A handwritten signature in black ink, appearing to read 'Charles M. Miller', with a long horizontal flourish extending to the right.

Charles M. Miller, MD
President

REFERENCES

- 1) Brockmann J1, Reddy S, Coussios C, Pigott D, Guirriero D, Hughes D, Morovat A, Roy D, Winter L, Friend PJ. Normothermic perfusion: a new paradigm for organ preservation. *Ann Surg.* 2009 Jul;250(1):1-6.
- 2) Ravikumar R, Jassem W, Mergental H, Heaton N, Mirza D, Perera MT, Quaglia A, Holroyd D, Vogel T, Coussios CC, Friend PJ. Liver transplantation after ex vivo normothermic machine preservation: a Phase 1 (first-in-man) clinical trial. *Am J Transplant.* 2016 Jan 11.