Guidance for the Content of Investigational Device Exemptions for Solutions for Hypothermic Flushing, Transport and Storage of Organs for Transplantation; Guidance for Industry and FDA Reviewers

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U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Gastroenterology and Renal Devices Branch
Division of Reproductive Abdominal and Radiological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Kathy Olvey, Gastroenterology and Renal Devices Branch, 9200 Corporate Boulevard, HFZ-470, Rockville, MD, 20850 or by email at kathleen.olvey@fda.hhs.gov.
Comments may not be acted upon by the Agency until the document is next revised or updated.

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This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

INTRODUCTION

This guidance is based on 1) current scientific knowledge, 2) clinical experience, 3) previous submissions by manufacturers to the FDA, 4) the Safe Medical Devices Act of 1990, 5) the FDA Modernization Act of 1997 and FDA regulations in the Code of Federal Regulations (CFR). As advances are made in science and medicine, and as changes occur in implementation of congressional legislation, these review criteria will be re-evaluated and revised as necessary.

General information regarding IDEs is provided in 21 CFR Part 812 as well as in the FDA "Investigational Device Exemptions Manual", and in a guidance document titled, "Guidance of IDE Policies and Procedures." These documents are available from the Division of Small Manufacturer's Assistance (DSMA) at (800) 638-2041 or on the internet at http://www.fda.gov/cdrh/manual/idemanul.html and http://www.fda.gov/cdrh/ode/idepolcy.html, respectively.

This document addresses solutions designed for flushing, transport and preservations of whole organs, including the kidney, liver, pancreas, heart and lung. It does not address solutions for preservation of the cornea, nor does it address the preservation of tissues (e.g., bone, cartilage, bone marrow, etc.) or cells (including pancreatic islet cells). It does not address machines designed for perfusion of donor organs.

Further guidance may be obtained through pre-IDE submission or meetings with the FDA. The FDA encourages all sponsors to arrange a pre-IDE meeting or teleconference whenever possible.

LEAST BURDENSOME APPROACH

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

In addition to the information described in the general IDE guidance documents listed above, the FDA recommends that all IDEs for these products contain the information described on the following pages.

I. DEVICE DESCRIPTION

A complete description of the solution should be provided. The description should address each of the following issues.

A. A listing of the chemical composition of the solution (including supplier and amounts) should be provided. All chemical components should be United States Pharmacopoeia (USP) grade. If not, adequate justification should be provided to demonstrate that the chemicals possess sufficient purity for use in this product.

B. An explanation of the purpose of each chemical component, (e.g., prevention of swelling, metabolic support, etc.) should be given.

C. The description should explain how the solution is to be used (e.g., for perfusion or static storage), highlighting any unusual features.

D. A description of the manufacturing process, including the method of sterilization, should be provided. The sterility assurance level and the results of sterility (i.e., endotoxin and bacteria) testing for at least one batch of product should be submitted.

E. A complete description of the packaging material should be provided. The packaging material should be appropriate for this intended use (i.e., blood or tissue contacting) therefore, biocompatibility testing as described in CDRH Blue Book memorandum G95-1, "Use of International Standard ISO-10993-1, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing" should be provided. In lieu of biocompatibility testing, the sponsor may identify a legally marketed product that uses the exact material for a similar intended use.

II. REPORTS OF PRIOR INVESTIGATIONS

IDEs for these products will typically require bench and animal testing prior to beginning a clinical study. Guidance for these tests is provided below.

A. Bench testing should address the stability of the product under both proper storage and worst-case conditions. A combination of real-time and accelerated test results may be acceptable for the IDE, however, real-time storage data should be submitted in any marketing application for these products. The stability testing should include analysis of all chemical constituents and any degradation products, measurement of particulate and assessment of sterility (bacteria and endotoxin) after storage for specified time periods. With regard to particulate, the solutions should meet USP specifications for large volume parenteral solutions.

B. Animal testing will normally be necessary to demonstrate the safety of the solution and, possibly, to establish the appropriateness of surrogate endpoints that may be used in the clinical trial. Separate animal studies will normally be necessary to demonstrate adequate preservation for each type of organ to be studied in the proposed clinical trial.

A complete description of the animal tests should be provided and should address the issues below.

1. A justification for the selected animal model should be provided, especially with regard to its relevance to the ultimate clinical use of the product. Although exploratory studies may be performed using a small animal model (e.g., mice), it is highly recommended that confirmatory studies be performed with a larger animal model (e.g., rabbits, pigs or dogs) to more closely approximate the expected clinical conditions.

2. Provide an explanation of specific organ performance parameters that will be evaluated, as well as a justification for their relevance in determining the safety and effectiveness of the proposed solution.

3. The investigational product should be tested against a control solution. It is recommended that the control be a solution that is widely used for preservation of the organ in question.

4. The results should be summarized in tabular and graphical format, with statistical analysis as appropriate.

C. Any clinical data obtained with the product, either in the U.S. or at foreign sites, should be supplied. If the data are described in literature articles, these should be provided. Foreign sites do not require IDE approval and are not required to be included in the IDE application, except as prior information to support the safety of the product or the applicability of the statistical analysis plan. However, clinical data obtained at foreign sites may be submitted in the marketing application as part of the primary data set. It is helpful for future marketing applications if the foreign sites use the same clinical protocol as the IDE study.

D. A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device should be provided along with copies of all published or unpublished adverse information.

III. INVESTIGATIONAL PLAN

A complete description of the investigational plan should be provided. As noted above, general recommendations on the content of IDE submissions is provided in the guidance documents referenced above. The following recommendations are provided in addition to the recommendations given in the general IDE guidance document.

The FDA strongly recommends that organ preservation solutions be studied in a multi-center, prospective, randomized, controlled trial. The control solution may be the solution currently in use at the investigational site (i.e., heterogeneous control) or the sponsor may select an appropriate control solution for all of the investigational sites (homogeneous control).

Data from foreign sites will be considered in any marketing application for this product. However, the data should be complete and should address all of the considerations outlined below. The FDA believes that it would be appropriate to include data from at least one U.S. investigational site in the marketing application, due to differences in clinical practice and patient outcomes between the U.S. and foreign transplantation centers.

In general, the number of patients and the number of sites should be determined using appropriate statistical analyses. However, the FDA recommends that the study include

at least three sites in order to capture potential differences among transplantation centers. The investigational plan should address the following:

A. Purpose of the Investigation

The purpose of the investigation should be provided. The sponsor should state whether they intend to demonstrate equivalence or superiority to the control solution. The sponsor should also state whether the organ preservation times are to be consistent with current clinical practice or if a claim of "extended preservation time" is desired.

B. Clinical Protocol

The clinical protocol should be described in detail, and should address the number of patients, the number of investigational sites, and the control solution to be utilized at each site (including the chemical composition). A complete listing of the inclusion/exclusion criteria should be provided, as well as the reasons for removal of the patients from the study or for termination of the study.

A description of the study endpoints should be given. The FDA recommends that the primary endpoint be 7 day patient survival for organ preservation solutions for the heart, lung and liver (specifically, 7-day ventilator or ECMO-free survival for lungs). The primary endpoint should be 7 day graft survival for solutions intended for preservation of the kidney.

In all cases, 30 day follow-up is strongly recommended, and 30 day survival should be tabulated and analyzed as a secondary endpoint. Additional secondary endpoints should be chosen to appropriately represent target organ function. For example, appropriate secondary endpoints for heart preservation solutions include cardiac index, wedge pressure, need for inotropic drugs, biopsy results and time in ICU. Appropriate secondary endpoints for kidney solutions are post-transplant creatinine and blood urea nitrogen (BUN) levels, histologic evidence of ATN, as well as need for post-transplant dialysis.

The protocol should address the expected preservation time for the organs. Studies designed to support claims of "extended" preservation time raise additional issues. Contact FDA to discuss these issues, if appropriate. Regardless of the intended claim, preservation times should be recorded for all organs in both the treatment and control groups.

C. Statistical Plan

A complete description of the statistical plan should be provided. The plan should address the sample size, proposed randomization scheme, proposed interim analysis and early stopping procedures (if applicable), poolability of the data and proposed analytical methods. Additional guidance on statistical methods for evaluation of clinical trial data is provided in "Statistical Guidance for Clinical Trials of Non-Diagnostic Medical Devices." A copy is available from DSMA or on the CDRH webpage at http://www.fda.gov/cdrh/ode/odeot476.html.