

Guidance for Industry

Somatic Cell Therapy for Cardiac Disease

DRAFT GUIDANCE

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Additional copies of this draft guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of this guidance, contact OCOD, CBER, at the phone numbers listed above or Sabina Reilly, Office of Device Evaluation, Center for Devices and Radiological Health, at 240-276-4095.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
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Additional copies of this guidance are available from:

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I. INTRODUCTION

This guidance provides you, sponsors who are developing cellular therapies for the treatment of cardiac disease, with recommendations on the design of preclinical¹ and clinical studies, and on the chemistry, manufacturing, and controls (CMC) information to include in an investigational new drug application (IND) for cardiac cellular therapy. This guidance also provides recommendations regarding the information that you should submit on the product's delivery system. Sponsors should consult with FDA concerning the regulatory pathway for the use of cell selection devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Despite advances in medical and surgical therapies, heart disease remains a major cause of morbidity and mortality. There is an increasing number of patients with significant morbidity despite optimal medical management. Cardiac cellular therapies have emerged as a field designed to advance the treatment of heart disease through the regeneration of cardiac tissues.

Cellular therapies for the treatment of cardiac disease generally meet the definition of "biological product" in section 351(i) of the Public Health Service Act (42 U.S.C. 262(i)), and are regulated by the Center for Biologics Evaluation and Research (CBER). Intravascular catheters and other

¹ For the purposes of this guidance, the term preclinical includes in vitro, in vivo and bench testing as described in Sections IV and V of the guidance.

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drug and biologic delivery systems generally meet the definition of “device” under section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(h)).

FDA expects that these cellular therapies and their dedicated delivery systems would meet the definition of a combination product under 21 CFR 3.2(e), either by being co-packaged or, if marketed separately, by using labeling that indicates they are intended for use together. Based on available information, the somatic cellular therapy generally would provide the primary mode of action of the combination product and the lead center typically would be CBER in accordance with 21 CFR 3.4.²

For a combination product, a single investigational application is generally sufficient. For cellular therapies and their dedicated delivery systems, this generally would be an IND. The IND application should contain the information as described in this guidance on the biological product and on the delivery system, along with any other information as required by the applicable regulations. CBER and CDRH intend to consult or collaborate on the IND review, as appropriate for the science and technology of the combination product.

For a combination product, one marketing application is also generally sufficient for FDA review and marketing authorization. However, sometimes two marketing applications may be necessary. You should consult with FDA regarding your particular product. FDA encourages sponsors to initiate a discussion regarding the number and type of marketing applications during product development. For additional information, see FDA “Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products.”

III. PRODUCT DESCRIPTION AND MANUFACTURING INFORMATION

Under Title 21 Code of Federal Regulations (CFR) 312.23(a)(7)(i), the CMC section of your IND must include sufficient information, as appropriate for the phase of the investigation, to assure the proper identification (identity testing), quality, purity, and strength (potency) of the investigational product. You must provide a description of the product and the manufacturing process, along with information concerning the safety and quality testing performed on the product prior to administration (21 CFR 312.23(a)(7)(iv)). The types of CMC information needed to support an IND for the use of cellular products in cardiac disease are similar to those required for cellular products for other indications. You should provide detailed descriptions of, and where necessary, data to support, the following:

- cell source
- collection methods
- processing methods

² Primary mode of action is defined at 21 CFR 3.2(m) and discussed in the final rule for *Definition of Primary Mode of Action of a Combination Product*, (Aug. 25, 2005, 70 Fed. Reg. 49848), available on the FDA’s website at <http://www.fda.gov/OHRMS/DOCKETS/98FR/05-16527.htm>.

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- ancillary materials
- formulation
- testing methods
- criteria to release cell product for administration
- storage/shipping conditions
- stability
- segregation procedures to prevent cross contamination
- container labeling (in process and final product)

One common processing step for cellular products is the use of immunomagnetic selection by means of monoclonal antibodies and paramagnetic microspheres to yield a cell population enriched for a specific cell surface antigen. Antibodies used in this process should be demonstrated to be free of adventitious agents and of appropriate quality to function as intended. You should also provide safety and quality information about the selection system/cell separation system that you have chosen. If these data exist in previous submissions to FDA by a sponsor other than yourself, you must obtain a letter of cross reference from that person to support the use of the selection system or antibody and submit this as part of your IND (21 CFR 312.23(b)).

For information concerning the data necessary to establish the biocompatibility of the cellular product with the delivery system please see Section V of this guidance.

For further information on the preparation of the CMC section of an IND, you may refer to the guidances entitled “Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)” and “Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy.”

IV. PRECLINICAL DATA AND TESTING

A. Preclinical Testing of Cellular Products for Cardiac Repair

Preclinical safety evaluation is required for all new investigational products prior to their use in clinical studies (21 CFR 312.23(a)(8)). Prior to initiating a clinical trial, you should provide sufficient preclinical data to establish a scientific rationale for clinical investigation of your product and to demonstrate an acceptable safety profile of your product and its delivery system. These data are generally derived from animal studies, although data from in vitro testing of the cellular product are often important in refining the animal study design. You should choose the most appropriate studies to demonstrate the activity and address the safety issues raised by your product. These safety issues could include issues raised by the chosen route of administration and the delivery system. We, FDA, encourage you to design testing strategies that combine testing of the cellular product and the delivery system in single studies if such a strategy does not compromise the validity of the collected measurements or the usefulness of the data.

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Generally, animal studies are used to assess the following:

- biological response to products (e.g., evidence of biological activity for proof-of-concept and safety studies)
- durability of response (e.g., length of time needed to assess the effect of treatment on the heart and the durability of that effect)
- toxicology (e.g., potential for local and systemic toxicities of the product). Local toxicities may be due to interactions of the product with the heart. Systemic toxicities may be due to cell migration outside of the pericardial area. The potential for tumorigenicity or inappropriate differentiation of cellular products may exist within the heart or in other locations where the product has migrated.
- dose response (e.g., effect of variation in cell number on cardiac repair or function)

The biological activity of cellular products *in vivo* is determined by their tissue of origin, level of differentiation, and extent of manufacturing (level of manipulation) in combination with the microenvironmental milieu in which they are placed *in vivo*. The tissue of origin, level of differentiation, and extent of manufacturing are characteristics unique to a particular product and can be controlled by the manufacturing process. However, the effects of microenvironmental cues on the biological action of a specific cellular product can only be assessed by use in animal models of cardiac disease. Such cues may be determined by the pathophysiology of the disease and the route of administration used for the cellular product.

Cellular therapies can be administered using several routes of administration and numerous delivery systems, (i.e., (1) direct, syringe-and-needle injection of cellular products through the exposed epicardial surface into the subjacent myocardium during concomitant thoracic surgery; (2) infusion of cellular products into coronary arteries; (3) intramyocardial injection of cell suspensions through cardiac catheters; and, (4) intravenous delivery). The route of administration will determine the final *in vivo* microenvironment of a cellular product and therefore affect its biological activity. The design of preclinical studies for these products typically includes an attempt to model the biological activities of a specific cellular product using the intended clinical delivery system in a specific clinical condition.

All preclinical studies that assess the ability of the delivery system to be deployed, to be retrieved, and to deliver the cellular product should evaluate the following device-specific endpoints:

- damage to the site of delivery system introduction/retrieval, the access vasculature, the site(s) of product delivery, and any significant intermediate structures (e.g., the aortic and/or mitral valve), using gross pathology and histopathology as appropriate;
- delivery system handling characteristics (e.g., flexibility, kink resistance, radiopacity, compatibility with accessory devices, and ease of insertion/removal); and
- damage to the delivery system as a result of simulated use.

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Studies performed in animals often require the use of either immunosuppressive agents to avoid rejection of the human cellular product or the use of analogous cellular products in animals. Analogous cellular products are cellular products derived from the animal species used for testing that are analogs of the ultimate clinical product in phenotype and biologic activity. You should characterize the level of analogy with the human product in preliminary studies prior to conducting the pivotal preclinical studies with the analogous cellular product. We recommend the use of pilot studies designed to confirm the suitability of testing a particular product in a specific animal species. Several animal studies and/or species may be necessary to adequately model functional aspects and potential toxicities of a single product. However, the number of studies needed should be determined by relevant biological characteristics of the product. All differences in manufacturing and the final product characteristics between the cellular product used in the animal studies and the product proposed for clinical use should be thoroughly described in the study report.

B. Model Selection and Data Reports

1. Use of In Vitro Data

In vitro data, i.e., immunophenotype or functional assays, can be used to make inferences about the potential activities of these cellular products. This information may in turn be used to direct the design and extent of the bench and animal testing needed to support a clinical trial.

2. Small Animal Models

Small animal models (e.g., immunodeficient or immunocompromised rodents) can provide information regarding the ability of the human cellular product to target the myocardium, as well as insight into potential safety issues related to the administered cells. These models can be used to study the potential for cellular products to survive and differentiate in the myocardium following infarction. However, they do not lend themselves to sensitive assessment of overall cardiac function or toxicities related to catheter administration of cellular products due to constraints of anatomy and physiology related mainly to body size.

3. Large Animal Models

Large animal models (e.g., pigs, sheep, and dogs) can provide information on the safety and activity of cellular products and the delivery systems, leading to the selection of a potentially safe starting dose for a Phase 1 clinical trial. In addition, these models can be used to address issues such as cell number, volume, rate of injection, and the optimal location for product administration. These data cannot be generated using small animal models due to the inability to directly test catheters for clinical use and the limited ability to monitor cardiac function.

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Large animal models of ischemia can be used to evaluate the activity and safety of cellular products following myocardial infarction. Models for non-ischemic congestive heart failure are more limited. Pathologies resulting from the commonly used methods for inducing cardiac ischemia (ligation, ameroid constriction and bead embolization) are not fully representative of the predominant mechanism of ischemia in humans, atherosclerotic coronary heart disease with vessel narrowing and collateral formation. However, these procedures are useful for modeling acute, subacute and chronic myocardial infarction in animals because they allow assessment of cellular products in ischemic microenvironments and ischemia-damaged tissues. Intramyocardial injection of cellular products may necessitate additional animal studies to explore factors contributing to the development of arrhythmias. These factors may include the composition of the cellular product, the dose of cells (absolute cell number and volume), and the site of cell implantation (with respect to anatomic features such as major conduction pathways or valves and to location within a scarred, ischemic area of myocardium).

4. Study Duration

The preclinical data package should include studies of sufficient duration to assess both acute toxicities within days of product administration and late toxicities that occur several weeks or months later. It is essential to assess late toxicities, which may be due to growth and remodeling of the cellular product within the cardiac wall.

5. Animal Report(s) to be Submitted in the IND

You should provide adequate information on any animal studies conducted using the investigational product, whether adverse or supportive, relevant to the evaluation of the safety of the investigational product. You must provide a full tabulation of data suitable for detailed review for each toxicology study that is intended primarily to support the safety of the proposed clinical investigation (21 CFR 312.23(a)(8)(ii)(b)). For each preclinical laboratory study subject to the Good Laboratory Practice (GLP) regulations under 21 CFR Part 58, you must include a statement that the study was conducted in compliance with the GLP regulations, or, if the study was not conducted in compliance with those regulations, you must provide a brief statement of the reason for the non-compliance (21 CFR 312.23(a)(8)(iii)) and you should specify any areas that deviate from the prospectively designed protocol and the potential impact of these deviations on study integrity.

For each preclinical report, you should describe the purpose of the study and provide a detailed methods section that includes information on the creation and location of the cardiac defect. Reports should include standard assessments, as well as, evaluations of pathological, histological, electrophysiological, and cardiac function.

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C. Leveraging Data

The amount, quality, and applicability of existing data (preclinical and clinical) for the cellular product, route of administration, and trial design that you intend to employ are factors that can influence the scope of the preclinical testing program. We recommend that you design your preclinical testing program following the principles provided in Section VIII of the “Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy” and any subsequent guidances that address the preclinical testing paradigms issued by the Center for Biologics Evaluation and Research. Ultimately the choice of the particular model(s) and overall preclinical study design should reflect the intended clinical situation. Early consultation with FDA to discuss applicability of a particular experimental approach, prior to its implementation, can be helpful. Additional information concerning the design of preclinical studies can be obtained from the March 18-19, 2004, Cellular, Tissue and Gene Therapies Advisory Committee (formerly Biological Response Modifiers Advisory Committee) meeting minutes.³

V. DELIVERY SYSTEM EVALUATION AND TESTING

The following sections describe the information that should be included in your IND to fully characterize the identity and performance of an intravascular catheter delivery system. Any other associated delivery methods, such as direct injection, should be fully described within the clinical protocol.

A. Regulatory Considerations

1. Master Files

If you plan to rely on data that concerns the performance of your delivery system and that is owned by another entity and contained in an IND, investigational device exemption (IDE), or master file, you must obtain and include in your submission a letter from the proprietary owner stating that FDA has permission to access this information (21 CFR 312.23(b)). This letter, referred to as a letter of cross reference, should state the location of this information within the file. You should also provide a scientific rationale that clearly explains why the leveraged data supports the performance of your delivery system and why any differences in evaluation conditions between the leveraged data and your proposed study do not affect the applicability of the leveraged data to the proposed study.

2. Identification

We recommend that you identify in your clinical protocol the device manufacturer, models, and sizes of the catheters to be used in your study. Additionally, we

³ Transcript available at <http://www.fda.gov/ohrms/dockets/ac/cber04.html>.

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recommend that you include a description of the catheter design requirements and a complete materials list.

3. Prior Information

Safety information regarding the use of your delivery system (including its use in situations similar to those in the current application) in the United States or abroad should be included. Safety information may be obtained from studies that you have conducted or from the literature. Safety information may also be contained in other files (INDs, IDEs, or master files) for which you have obtained a letter of cross reference.

4. Risk Analysis

You should provide in your IND a scientific rationale, incorporating available preclinical and clinical data, which demonstrates that the use of your delivery system does not constitute an undue risk to the patient. This rationale should include a risk analysis based on the design and intended use of the delivery system that assesses the risks posed to the patient by the delivery system. For each risk, you should describe what measures, if any, you have taken or will take to mitigate that risk.

B. Preclinical Testing of the Delivery System

We recommend that you evaluate the performance of your delivery system using a battery of in vitro and in vivo tests. Testing should demonstrate that the delivery system is capable of safely delivering the cellular product according to the specifications provided in the clinical protocol. Your preclinical test regimen should incorporate the following recommendations.

1. Test Conditions

Any testing should simulate the clinical delivery procedure as closely as possible and should evaluate the full range of delivery systems used in the study. For variables such as product concentration and/or volume, delivery pressure/flow rate, and the number of delivery steps, testing should also be conducted using worst-case clinical conditions as specified in the clinical protocol, unless otherwise specified.

2. Data Reporting

When describing the preclinical tests, you should provide the following information.

- a description of the test protocol;
- the number and sizes of the samples tested;

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- the acceptance criteria, including the clinical relevance of the criteria;
- the test results, including average values and data ranges; and
- the conclusions you drew from the test results.

3. In Vitro Testing

We recommend that you evaluate the mechanical performance of the delivery system using in vitro models to ensure that the delivery system can safely and effectively deliver biological products. Typically, in vitro testing establishes the performance limits of the delivery system. As such, satisfactory in vivo data does not necessarily obviate the need for in vitro testing.

Currently, the scientific literature demonstrates the feasibility of two concepts for catheter based delivery of cellular products:

- infusion of cell suspensions into the coronary vasculature that supplies the target region of myocardium; and
- injection of cell suspensions directly into the target region of myocardium using catheters that contain injection needles.

Other concepts for catheter delivery of cellular therapies may be feasible. Since delivery systems can involve various principles of operation, your risk analysis should explain in detail why the preclinical test regimens selected are applicable to your delivery system, and that these tests are sufficient to assess the preclinical performance of the device. You may wish to consult with the FDA concerning the relevant performance tests for your device. Please see the Appendix for additional information concerning in vitro testing of your delivery device.

4. Delivery System-Patient Biocompatibility

We recommend that you demonstrate that the patient-contacting materials of the delivery system do not provoke a harmful biological response. To assess the risks related to the materials used in the construction, processing, and storage of the delivery system, we recommend that you consult the guidance document entitled “Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices, Blue Book Memo, G95-1” (Ref. 1). In addition to the guidelines provided, we recommend that you evaluate the materials-mediated pyrogenicity of the delivery system, or explain why such evaluation is not necessary.

5. Delivery System-Product Biocompatibility

To demonstrate that the delivery system can deliver the cellular product without damage to either the delivery system or the product, you should evaluate cell viability/activity, cell adhesion to the device, and device integrity using an in vitro model that accurately mimics the clinical protocol. Because biologics can aggregate

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and adhere more easily at low flow rates, the worst-case delivery rate for this test may differ from that used in the other preclinical tests. Further, because cellular products can possess extremely variable sensitivities to physical and chemical stimuli, you should repeat these tests for each new delivery system-product combination. If you plan to leverage compatibility data which uses a different delivery system-product combination, you should provide a detailed and specific scientific rationale for the applicability of this data.

6. Preclinical In Vivo Studies

Please see discussion of recommended animal models for preclinical testing of the study product and its delivery system under Section IV above.

7. Sterilization

FDA recommends that you provide sterilization information in accordance with the CDRH “Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA” (Ref. 2). You should sterilize the device to a sterility assurance level of 1×10^{-6} using a sterilization cycle that has been validated in accordance with the quality systems regulations (see 21 CFR Part 820).

We recommend you test the devices for pyrogenicity. We also recommend that you provide the following:

- description of the method used to make the determination, e.g., limulus amoebocyte lysate;
- identification of the testing endpoint reached and rationale for selecting that endpoint;
- description of the extraction technique used to obtain the test fluid from the test device, showing that all clinically relevant contact surfaces of the test device were assessed; and
- identification of the reference method used, e.g., ANSI/AAMI ST72 or FDA guidance.

8. Shelf Life

FDA recommends that shelf life testing address package integrity to ensure sterility, as well as stable device functionality over the expected life cycle. To evaluate device functionality, we recommend that you assess each of the bench tests described in the Appendix and repeat all tests that evaluate design characteristics affected by aging. We also recommend that you provide the protocol used for your shelf life testing, the results of the testing, and the conclusions drawn from your results.

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C. Catheter Labeling

You should submit clear and concise instructions that delineate the technological features of the specific device and how the device is to be used. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and with its safe and effective use.

VI. CLINICAL TRIAL DESIGN

Standard elements of clinical trial design include patient selection, product administration, safety monitoring, and the choice of appropriate endpoints and control populations. An overall development program should also include clearly defined criteria concerning the type and level of product activity that will lead to further development. When designing a clinical trial, the product's mechanism of action, as well as any additional information that may be learned concerning the mechanism of action, should also be considered. This may impact your selection of the primary endpoint as well as your evaluation of consistency among multiple endpoints. An additional element in the use of cellular therapies, particularly those involving autologous products, is that the same number of a pure population of well characterized cells is rarely administered to each subject. This will complicate the interpretation of the product's activity and mechanism of action and should be considered in the trial design.

A. Subject Population

1. Refractory Angina/Ischemia

Trials that recruit subjects with refractory angina while on optimal medical therapy should provide criteria for and documentation of the patient's medical therapy and the frequency and severity of angina. For example, the trial may require that subjects have a specified class of angina as defined in a standard classification (e.g., Canadian Cardiovascular Society class), experience a given number of angina episodes per week, or develop angina on exercise testing. You may choose to have subjects document the number of episodes of angina per week through the use of an angina diary. Criteria for optimal medical therapy should be consistent with current, evidence-based American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Documentation of the subject's response to these medications (angina despite the use of optimal dosing or the inability to tolerate certain classes or doses of anti-anginal medications, etc.) may be obtained by the use of a run in period or through an accurate medical history at study entry.

Trials that recruit subjects with refractory myocardial ischemia should describe the means of ascertaining ischemia (e.g., single photon emission computed tomography (SPECT) scanning or other imaging modalities). You should document the presence of ischemia through the use of a standardized test (e.g., exercise tolerance test) with an endpoint such as the onset of electrocardiogram (EKG)-demonstrated ischemia.

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Additionally, many trials in the treatment of chronic ischemia require that subjects not be candidates for percutaneous or surgical coronary intervention. This should be determined by an interventional cardiologist (percutaneous intervention) or a cardiothoracic surgeon (surgical intervention) prior to study entry.

2. Acute Ischemia/Infarction

Trials that recruit subjects with acute ischemia or those in the peri-infarct period should employ clear definitions of these events (such as the standardized definitions adopted by the ACC/AHA). The time interval between the onset of symptoms and product administration should be specified along with the use of background medical therapies that are in accordance with ACC/AHA guidelines. Safety should be a clear focus since these subjects are at high risk for additional cardiac events. In these trials, you may choose to administer the study product alone (in subjects who are not candidates for additional intervention) or in combination with stenting, angioplasty, coronary bypass grafting, etc. The indication for these interventions (ongoing angina, congestive heart failure) may dictate the need for additional entry criteria.

3. Heart Failure

Trials that recruit subjects with symptomatic heart failure despite optimal medical therapy should provide criteria for and documentation of the severity of the patient's heart failure and the medical management of this condition. New York Heart Association classification is commonly used in the categorization of congestive heart failure. This classification is subjective and can lead to erroneous conclusions in a small randomized trial. Similarly, the clinical relevance of absolute cutoff values for the cardiac ejection fraction at study entry is unclear. You may, therefore, wish to consider the use of more quantitative measures such as cardiopulmonary exercise testing in establishing your entry requirements. Criteria for optimal medical therapy should be consistent with current, evidence-based ACC/AHA guidelines and should be documented (e.g., on the case report form).

4. General Requirements

You should also provide criteria for the occurrence of recent cardiac events (myocardial infarction, non-Q wave infarction), the timing of prior cardiac catheterization, and the presence of co-morbid conditions which may increase patient risk or limit cardiac function. In addition, trials which administer product directly into the myocardial wall should provide criteria for wall thickness and the presence or absence of scar tissue at the site of injection. In general, wall thickness at the site(s) of injection should be twice the length of maximal needle deployment. Finally, if you anticipate that a drug-eluting coronary stent will be implanted, you should consider whether the eluted drug(s) could negatively impact the viability and activity of the cellular product and modify your eligibility criteria accordingly.

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B. Product Administration

You should provide a detailed description of product administration. This may include:

- the method used to determine the site(s) of injection, record their location(s), and to match the site(s) chosen with those injected;
- the proposed number of injections (total and per cardiac wall) or the number of balloon inflations and their duration;
- the concentration, volume (total and per injection), and flow rate of the cellular product, and;
- the method of product delivery, either through direct injection or through the use of a delivery device. If a delivery device is used, detailed information concerning its delivery and retrieval from the site of injection should be provided.

Product administration may be documented through the use of anatomic drawings, written descriptions, or films of the injection procedure during catheterization.

C. Safety Monitoring

You must follow applicable reporting requirements outlined in 21 CFR 312.32 for adverse experiences associated with the use of the product. Additional information concerning Good Clinical Practice can be found in the “Guidance for Industry: ICH E6 Good Clinical Practice: Consolidated Guidance.” You should record and report to FDA all procedure-related and biologic-related adverse experiences, including both immediate and long-term adverse experiences. Long-term complications of particular interest include death, arrhythmias, neurological events, and adverse experiences thought (mechanistically) to be associated with the biologic product. You should prospectively define these adverse experiences and include them in the trial protocol to guide investigators, monitors, and clinical events committees.

1. Cardiac Enzymes

We recommend that cardiac enzymes be obtained pre-procedure and that serial determinations be obtained following the procedure in all subjects. There is no accepted consensus concerning the level of cardiac enzymes that is indicative of a clinically important event following an interventional procedure. You should, therefore, monitor cardiac enzymes and include them in your study stopping rules.

2. Arrhythmias and Conduction Abnormalities

The cardiac rhythm should be monitored during the procedure and subjects should be placed on telemetry following the procedure. In addition, serial EKGs should be performed. In reporting these arrhythmias, a distinction should be made between isolated ventricular ectopy during product administration and more complex or sustained arrhythmias. At each clinical visit, you should focus on a history of

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palpitations, chest pain, dyspnea, fatigue, lightheadedness, or syncope in an effort to identify subjects with arrhythmia. Holter monitoring (or a similar system) should be considered in all subjects. If episodes are infrequent, an event recorder, which allows the patient to transmit the EKG to a recording facility when the arrhythmia occurs, may be more useful. Special attention should be given to subjects receiving skeletal or cardiac myoblasts. These subjects should undergo serial monitoring of their cardiac rhythm (e.g., with a Holter monitor) regardless of symptoms. Consideration should also be given to the placement, prior to the administration of the cellular product, of an automatic implantable cardioverter-defibrillator in subjects with a significant history of arrhythmia or a decreased ejection fraction.

3. Myocardial Perforation/Pericardial Effusion

To monitor for the development of a pericardial effusion following product administration, you should perform post-procedural echocardiography (or another study capable of detecting a pericardial effusion) in subjects undergoing percutaneous injection of the cellular product into the cardiac wall. These studies should be obtained immediately following the procedure and then at 4 to 6 hours post procedure. Abnormal findings should be followed to resolution.

4. Unique Monitoring Requirements

Cellular therapies may include the administration of autologous or allogeneic cells. You should monitor subjects receiving allogeneic cells for the development of a cellular and a humoral immune response. It may take several weeks for the host to develop an immune response to allogeneic cells. Further, these cells may grow and differentiate within the host resulting in a change in the level or expression of cell surface markers and altering the immune response. The timing of the blood samples to assess this response is critical. In addition to laboratory testing, subjects should be monitored for the development of a clinical immune response. An additional consideration is those subjects who may require a future cardiac transplantation. Allogeneic cells should be used with caution in these subjects since they may sensitize them to additional human antigens.

5. Stopping Rules

We recommend that all protocols for the use of cellular therapies in the treatment of cardiac disease contain stopping rules. These stopping rules should address the considerations discussed in Section VI.A.3, as well as those issues unique to the product and its method of delivery.

6. Duration of Follow-Up

Since the purported mechanism of action of these products involves tissue remodeling and integration, long-term follow-up is essential. Long-term follow-up should

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include both the evaluation of late adverse events and the persistent activity of the product. The establishment of long-term activity is fundamental to the assessment of the risk-benefit ratio. The timing of endpoint assessment and the duration of follow-up may vary with the product and its indication. In many instances, the long-term outcome should be assessed prior to product approval while in other instances, additional information concerning long-term outcome may be submitted following licensure. You should provide a long-term follow-up plan within the protocol.

D. Study Endpoints

You should carefully consider the product's expected mechanism of action and the indication you are seeking in your choice of study endpoint(s). In early trials, you may wish to examine a small number of endpoints, choosing one or more of these as the primary endpoint(s) in your Phase 3 studies. This will allow you to evaluate various methods of assessment and to determine the degree of variability in the study product and in this endpoint. In Phase 3 or in earlier studies, you may wish to utilize one or more of the following: (1) an evaluator who is independent of the study team; (2) a clinical events committee; or (3) a core laboratory. The primary endpoint chosen for Phase 3 studies should establish the clinical benefit of your product. Further information may be obtained from the "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products."

1. Refractory Angina/Ischemia

You should carefully consider the indication for use in seeking a claim in subjects with refractory ischemia. For example, an exercise tolerance test which measures the time to the development of angina may be used for an angina indication. However, exercise tolerance testing should also examine the time to 1 mm ST depression. Additional endpoints that may be of value in a blinded study include, but are not limited to, Canadian Cardiovascular Society angina class, and angina diaries. You may also consider the use of secondary endpoints such as exercise test duration and change in SPECT imaging or echo wall motion scores.

2. Acute Ischemia/Infarction

Trials designed to test the product's effect on acute myocardial ischemia or the return of function post myocardial infarction may consider endpoints such as mortality, number of subsequent cardiovascular hospitalizations, or exercise tolerance testing which measures the time to angina and 1 mm ST depression. Additional endpoints which may be of value in a blinded study include, but are not limited to New York Heart Association class, Canadian Cardiovascular Society angina class, and angina diaries. With each of these endpoints, you should consider the contribution of early death to the analysis of this endpoint and to the number of subjects enrolled in your study. You may also consider the use of secondary endpoints such as change in single photon emission computed tomography imaging, echo wall motion scores, or

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infarct size. When selecting an endpoint for use in these studies, you should also consider the relative contribution of additional interventions (e.g., stent placement, bypass grafting) to patient outcome.

3. Heart Failure

Trials designed to test the product's effect on heart failure may consider endpoints such as mortality, the number of subsequent cardiovascular hospitalizations, cardiopulmonary exercise testing, six minute walk, and the need for various interventions (e.g., an implantable defibrillator, left ventricular assist device, transplantation). In general, endpoints such as mortality and cardiovascular hospitalizations should be utilized in Phase 3 studies. Additional endpoints which may be of value in a blinded study include, but are not limited to, New York Heart Association class or validated patient reported outcome questionnaires. Each of these endpoints should be carefully considered in terms of the long- and short-term risk-benefit ratio of the product. You may also consider the use of secondary endpoints such as change in left ventricular mass and left ventricular dimensions which are suggestive of reverse remodeling.

4. Unique Endpoint Considerations

Elements unique to the design of clinical trials involving cellular therapies include the duration of follow up and the effect of product variability on outcome. The need for tissue remodeling and integration with many of these products suggests that optimal function may be obtained many months after product administration. This should be assessed during early trials and considered in the timing of endpoint assessment in Phase 3 studies. The need to demonstrate long-term outcome should also be considered. To adequately assess the risk-benefit ratio of these products, all studies of cellular therapy in cardiac disease should, in general, follow subjects for survival.

Cellular therapies, particularly those involving an autologous product, rarely administer the same number of a pure population of well characterized cells to each subject. Therefore, early trials should be designed to assess the level of variability in product manufacture and to examine subject response in terms of the number, type, and location of the administered cells. In many instances, too few subjects will be available in each group. One possibility is the use of preclinical models to identify the parameters that are essential to the activity of the product and to address these issues in early clinical trials. The successful conduct of Phase 3 trials depends upon accurate assessment of variability in the treatment effect.

E. Choice of Control

Trials for the treatment of cardiac disease have the potential for bias, including positive and negative placebo effects, treatment bias, and assessment bias. Because of this, randomization to active treatment or to a well-constructed control is one of the most

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important issues in trial design. The choice of controls will determine product labeling, sample size, the hypothesis tested (e.g., superiority versus non-inferiority), and the study endpoint(s)). In general, the control group should reflect the current standard of care in a particular disease setting. The experimental therapy may then be compared to the standard of care or used in an “add on” design in which subjects receive standard treatment with or without the experimental therapy. A detailed discussion on this is available in the “Guidance for Industry: ICH E10 Choice of Control Group and Related Issues in Clinical Trials.”

While control arms are essential in Phase 3 trials, the use of a control arm may be considered in early trials if their use would lead to valuable conclusions concerning product safety and activity. However, a control arm should only be used if meaningful conclusions can be drawn (i.e., the trial is of sufficient size).

1. Controls for Surgical Administration

In general, we do not recommend that a surgical procedure be performed solely for the placement of cellular therapy. However, an “add on” design in which cellular therapy is administered at the time of the surgical procedure and the blind maintained by use of placebo injections or a separate team to perform post-procedure patient care and endpoint assessment is acceptable.

2. Controls for Percutaneous Administration

If a percutaneous procedure, transendomyocardial or intracoronary administration with balloon inflation is performed solely for the delivery of cellular therapy, the risk-benefit ratio of this procedure should be carefully considered. Depending on the risk involved, you may consider incorporating a control procedure into your trial. An example of such a control procedure is the use of sham cardiac catheterization in which control subjects undergo femoral artery access and the catheter is positioned in the aorta or left ventricle while the staff performs activities similar to those in the active arm.

“Sham controlled studies” represent one study design and choice of control group which may allow for discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors such as patient or observer expectations. This type of study design could be considered in studies with subjective endpoints such as reduction in patient-reported symptoms. Sham surgical procedures/treatments involve more risk than the placebo control arm in drug trials and should be used in limited circumstances. This study design should only be considered when it is methodologically necessary, i.e. when designs that are unblinded are methodologically unacceptable (e.g., because endpoints are subjective) and when a “no treatment” control is methodologically required. Furthermore, the withholding of treatment should not lead to serious harm, such as death or irreversible morbidity. FDA recognizes that it may be difficult for sponsors to develop a clinical study design

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with a sham control arm that investigators, institutional review boards, and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully considered and planned. Additionally, if a sham procedure/treatment is being considered in a clinical investigation involving children, the requirements of 21 CFR Part 50 Subpart D (Subpart D) also apply. If you choose a sham-controlled trial, you should give careful consideration to maintaining the blinded nature of your trial for the subjects and physicians. In order to maintain this blind, a separate assessment team may be needed to perform post-procedure subject care and endpoint assessment.

Percutaneous administration may also be used in an “add on” design. Again, the risk-benefit ratio of the administration of the cellular product should be evaluated and the use of various controls carefully considered. Finally, you may wish to use a design in which subjects are randomized to cellular therapy or best supportive care. If this alternative is chosen, careful attention should be paid to the selection of endpoints which are not subject to bias.

F. Informed Consent in Trials Involving Long-term Follow-up Observations

Long-term follow-up observations will help to fully assess the results of tissue integration and differentiation of the cellular product. This allows the collection of, as yet, uncharacterized late adverse experiences and provides an assessment of product risk (and the risk of product administration) in terms of persistent benefit. In general, long-term follow-up observations should be built into all phases of these trials.

The informed consent document must describe, among other things, the purposes of the research and the expected duration of the subject’s participation and the procedures to be followed (21 CFR 50.25(a)(1)). Accordingly, the informed consent document must explain the purpose and duration of long-term follow-up observations, including the time intervals and location/method of subject contact (21 CFR 50.25).

G. Statistical Considerations

For late phase studies, the statistical analysis plan should clearly define the primary endpoint, the primary analysis population, and the test statistic that will be used to analyze the primary endpoint. In general, the primary efficacy analysis should be conducted in the intent-to-treat population. The method that will be used to handle missing data in this analysis should be pre-specified. If missing data are imputed, this should be supported by a series of sensitivity analyses in which a variety of imputation methods are used, including a worst case scenario. In trials that involve subjects with acute myocardial infarction, you should also pre-specify the statistical handling of subjects who die before the time of efficacy endpoint assessment. (Note: a large amount of missing data may make the results of any trial difficult to interpret).

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It is essential that your statistical analysis plan address each of the relevant elements, eligibility, administration, safety monitoring, and endpoint assessment discussed in Section VI. For example, you may wish to stratify by key inclusion criteria or by variables such as the investigator performing the procedure. You should also include analyses of variability in the product and its site(s) of implantation as exploratory analyses in your statistical analysis plan. Inconsistencies in endpoint assessment can be minimized by performing several measurements (e.g., repeat exercise tolerance tests). Finally, given the importance of bias in these studies, you should consider an assessment of blinding and then utilize this information in an exploratory analysis of your primary endpoint.

The primary safety analysis should be conducted in all subjects who underwent a study procedure whether or not they received study product. Additional analyses may be necessary in all subjects who received study product. You may also wish to include analyses of adverse events thought to be related to the procedure and adverse events thought to be related to the cellular product. Your proposal for these analyses should be provided in your statistical analysis plan.

In early trials, the use of multiple secondary endpoints may lead to inaccurate conclusions concerning product activity in studies that fail to meet their primary endpoint. If you wish to include secondary endpoints in product labeling, their method of analysis along with a hierarchical plan for alpha spending should be included in the statistical analysis plan. Please note that the findings from the primary analysis, all secondary analyses, and all safety analyses, as well as all exploratory analyses will be examined in determining the suitability of a product for licensure. The “Guidance for Industry: ICH E9 Statistical Principles for Clinical Trials” provides an extensive discussion on statistical considerations for the design and analysis of clinical trials. We also recommend that you interact with FDA early in the trial design process to collaborate on an analysis plan.

VII. REFERENCES

1. Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices, Blue Book Memo, G95-1, May 1995 (<http://www.fda.gov/cdrh/g951.html>).
2. Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA, August 2002 (<http://www.fda.gov/cdrh/ode/guidance/361.html>).

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APPENDIX: In Vitro Testing of the Delivery Device

Since some polymers may soften at body temperature, we recommend that you perform in vitro testing under conditions simulating clinical use. For example, prior to evaluation of each parameter, you should submerge the catheter in a saline bath at 37°C for a duration consistent with the intended use, or pass the catheter through a U-shaped tube to simulate tracking over the aortic arch or other severe bend. As part of your test report, you should describe the rationale for your choice of the vascular model and the effects of the model dimensions. Additionally, you should include a schematic, drawing, and/or photograph of the test apparatus.

Your preclinical test regimen should assess the following characteristics using a clinically relevant in vitro model. Not all of these performance characteristics may be applicable to your delivery system and the assessment of additional performance characteristics may be appropriate.

Dimensional verification: You should ensure that the device dimensions meet specifications previously determined to ensure acceptable performance. Key device dimensions may include the catheter length and profile, the length and diameter of injection needles, and the length of balloon components.

Burst pressure: The catheter body should be designed to withstand pressures typically needed to achieve media flow rates used in clinical practice. You should determine the pressure beyond which the device is expected to leak or rupture. You should also describe the mode(s) by which the delivery system fails at the specified pressure, such as rupture of the delivery shaft or leakage of specific seals.

Flow rate: The catheter should be designed to achieve clinically acceptable media flow rates. We recommend that testing be done at maximum catheter burst pressures (as identified in the test described above), as well as pressures typical of clinical use. We recommend that you report the maximum flow rate in the device labeling. We also recommend that you provide the clinical basis for your acceptance criteria.

Bond Strength

- **Tensile/bending strength**: You should characterize the resistance of your delivery system to tensile (pulling) and bending (flexion) forces. You should test the bond strength at any location where adhesives, thermal fusion, or other joining methods are used for bonding sub-components of the device.
- **Torsional strength**: You should characterize the resistance of your delivery system to torsional (twisting) forces. You should test the bond strength at any location where adhesives, thermal fusion, or other joining methods are used for bonding components of the device. We recommend that you report the number of rotations to failure and the failure mode for each sample tested. Additionally, we recommend that you report the number of turns to failure in the device labeling.

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Fatigue: You should ensure that the delivery system can repeatedly deliver accurate quantities of cellular product without degradation of performance or structural damage. You should base the number of fatigue cycles on the number expected clinically, plus an appropriate safety margin. If your device incorporates a retractable tip, you should ensure that the tip can be extended and retracted without failure to the clinically anticipated number of cycles, plus an appropriate safety margin. Additionally, you should conduct this test in both deflected (where applicable) and non-deflected states to simulate actual clinical use.

Stiffness: To assess the stiffness or flexibility of the complete device, we recommend that you measure the deflection of the device for a given force applied to the center point of the catheter shaft when the catheter is suspended between the tip and the catheter/handle junction. We recommend that you measure the force required to cause a finished, undeflected catheter to buckle. The buckling force should not be so large that your delivery system presents a high risk of vessel perforation or dissection.

Radiopacity: We recommend that you determine the ability of the operator to observe the device using fluoroscopy or other imaging modalities.

For Deflectable Catheters:

- **Steering and Deflection Cycle Test:** For devices designed to be deflected to aid with steering through the vasculature, we recommend that you demonstrate that the catheter can withstand a clinically relevant number of complete actuations of the deflection mechanism without failure, plus an appropriate safety margin.
- **Deflection Force Test:** For devices designed to be deflected during use, you should measure the applied force on the distal tip when the device is deflected to 90° during full actuation of the deflection mechanism in the absence of any other catheter movement. You should explain how you constrained the catheter during this test, and why this method was appropriate.
- **Applied Force:** For devices designed to be deflected, we recommend that you compute statistics for the applied force on the distal tip from the 90° position, both during full actuation of the deflection mechanism without translation (tracking or retrieval), and also as a result of translation of the catheter without further deflection, for the various curve configurations.

Cable/Connector Separation Test: If operation of your device requires mechanical or electrical connections to accessory devices, we recommend that you determine the reliability of the connection between the device proximal connectors for each connector type. This test should be performed by developing a test protocol that simulates device use and then testing to ensure that the connectors remain connected during normal use.

Balloon Performance

If your device incorporates one or more balloon components, you should ensure that the balloon can be used safely and according to device specifications. Depending on the design of your device, the following balloon performance characteristics may be applicable.

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- Balloon fatigue – You should ensure that the balloon can be repeatedly inflated and deflated without malfunction or structural damage. The number of fatigue cycles should be based on the number expected clinically, plus an appropriate safety margin.
- Balloon inflation/deflation time – You should ensure that the balloon can be inflated and deflated within clinically acceptable time frames.
- Balloon burst – You should determine the inflation pressure or volume at which the balloon is expected to leak or rupture.
- Balloon compliance – You should characterize the extent of inflation of the balloon as a function of the volume or pressure used for inflation. This information will assist the operator in determining the proper degree of inflation for each patient treated.