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Regenerative Medicine Clinical Trials: US FDA Supports Studies Comparing Multiple Agents

by Brenda Sandburg

Draft guidance suggests comparing therapies for a rare disease to each other and active control, offers examples of novel efficacy endpoints and what therapies may qualify for breakthrough and RMAT designations.

The US FDA is encouraging the use of adaptive clinical trial designs for regenerative medicine therapies, such as having sponsors study several investigational agents together for treatment of rare diseases.

The Center for Biologics Evaluation and Research describes its views on clinical trial designs in a *draft guidance*, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, released Nov. 16.

FDA Commissioner Scott Gottlieb and CBER Director Peter Marks announced the issuance of four guidance documents and the agency's new policy approach to facilitating the development of innovative regenerative medicine products in a media call.

"Our goal is to make sure we are being nimble and creative when it comes to fostering innovation, while taking steps to protect the safety of patients," Gottlieb stated. He noted that the agency is proposing novel and innovative approaches to regulation to meet the revolutionary nature of the products it is being asked to evaluate.

For example, Gottlieb said that the agency is considering a trial design whereby individual academic investigators would follow the same manufacturing protocols and share combined clinical trial data in support of FDA approval.

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The expedited programs guidance notes that CBER intends to work with sponsors to encourage flexibility in clinical trial design. "We will consider clinical trials in support of a BLA that incorporate adaptive designs, enrichment strategies, or novel endpoints," the guidance says.

Sharing Combined Clinical Data

The agency notes that for some rare diseases there will likely be a limited number of affected people eligible to enroll in clinical trials and suggests sponsors work together. "Innovative trial designs, such as trials that compare several different investigational agents to each other and a common control, may be particularly useful in studies of regenerative medicine therapies to treat rare diseases," the guidance says.

For more common diseases, FDA says it might be appropriate for multiple clinical sites participating in a multi-center trial to share the combined clinical trial data to support BLAs. "In such trials, manufacturing would be performed at all clinical sites using a common manufacturing protocol and product quality testing specifications," the guidance states.

"For example, this trial design could be considered for the use of stem cells derived from adipose tissue for the treatment of debilitating osteoarthritis, whereby the trials are conducted at a specified number of orthopedic practices. In this situation, each practice could submit a BLA that relies on both the data from the individual practice and the combined data from all practices that participated in the clinical trial."

BlueRock Therapeutics CEO Emile Nuwaysir said companies in the regenerative medicine space are excited about getting more clarity from FDA and seeing the agency streamline the approval process.

Regarding the use of combined clinical trial data, Derek Hei, BlueRock Therapeutics' Senior VP of Manufacturing, Quality & Regulatory, said having individual academics or small investigators work together under the same protocol and share data is an interesting idea but he noted that it is challenging to get the same product made at multiple sites.

BlueRock is developing allogeneic cell therapies to replace damaged or dysfunctional cells. It expects to file an IND next year for treatment of Parkinson's disease with purified dopaminergic neurons.

Short-Term Performance As Novel Endpoint

The agency said it would also work with sponsors to determine the types of endpoints that might be appropriate for various phases of clinical development. The guidance gives two examples of novel endpoints: improvement in visual function as evidence of effectiveness for treatment of conditions that lead to visual impairment; and short-term performance for regenerative medicine therapies that are cellular or tissue constructs intended to replace a tissue or organ.

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The guidance recommends that sponsors talk with the Office of Tissues and Advanced Therapies review staff early in product development.

The document describes the expedited programs for regenerative therapies, including the regenerative medicine advanced therapy (RMAT) designation, which was created by the 21st Century Cures Act that became law in December. The agency provided a brief description of how products may qualify for the designation in a notice posted on its website in January. (Also see "*RAT Race Begins: FDA Accepting Regenerative Advanced Therapy Designation Requests*" - Pink Sheet, 30 Jan, 2017.)

How To Get An RMAT Designation

The draft guidance gives details on the use of the breakthrough therapy designation for regenerative medicine therapies and the RMAT designation and includes examples of when products may qualify for each designation.

> ***As of Nov. 9, CBER had received 31 requests for the RMAT designation and granted 11 of them.***

Therapies that CBER may consider for breakthrough therapy designation include treatment for metastatic breast cancer that is refractory to available therapies in which allogeneic tumor cell lines expressing tumor-specific antigens are associated with complete clinical responses in a substantial portion of the study subjects in an open-label, first-in-human study.

To be eligible for RMAT designation, an investigational drug must meet the definition of regenerative medicine therapy; be intended to treat, modify, reverse or cure a serious condition; and have preliminary clinical evidence that indicates it has the potential to address unmet medical needs.

When determining whether preliminary clinical evidence is sufficient to support an RMAT designation, CBER will consider such factors as the rigor of data collection; the nature and meaningfulness of the outcomes; the number of patients or subjects; the number of sites contributing the data; and the severity, rarity, or prevalence of the condition. The guidance says that unlike the breakthrough therapy designation, the RMAT designation does not require

evidence to indicate that the drug may offer a substantial improvement over available therapies.

The guidance cites two hypothetical examples of preliminary clinical evidence that CBER would consider to be sufficient to demonstrate a product has the potential to address unmet medical needs in those with a serious condition.

One of these is a single-arm, open-label study conducted in a center treating patients with severe and extensive skin burns in which use of allogeneic keratinocyte- and fibroblast-based cell therapy is associated with rapid and substantial wound re-epithelialization of deep partial thickness burns in the majority of treated wounds.

The guidance says CBER will not accept requests for RMAT designation for investigational new drugs that are inactive or on clinical hold. The Center will notify the sponsor if it will be given the designation no later than 60 calendar days after receiving the request.

As of Nov. 9, CBER had received 31 requests for the RMAT designation and granted 11 of them.

Humacyte Inc. was the first company to receive the designation, which was granted for its bioengineered blood vessel *Humacyl*. *Enzyvant Sciences Ltd.* also received the designation for its tissue-based biologic therapy RVT-802. (Also see "*Regenerative Medicines Provisions Of Cures Act A Top Priority For CBER*" - Pink Sheet, 9 Jun, 2017.)

CBER Director Peter Marks noted at meeting in September that FDA discussions with sponsors on RMATs are more focused on manufacturing issues, which he said are very complicated for many of the products. (Also see "*RMAT Designation Enables Critical Manufacturing Discussions – FDA's Marks*" - Pink Sheet, 12 Sep, 2017.)

Device-Therapy Combo Guidance

In addition to the expedited programs draft guidance, the agency issued three other guidance documents pertaining to regenerative medicine.

A *draft guidance* on Evaluation of Devices Used With Regenerative Medicine Advanced Therapies addresses how FDA intends to simplify and streamline its application of regulatory requirements for

Devices Addressed In US FDA's New Regenerative Medicine Framework

By Elizabeth Orr

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The framework includes two draft guidance documents and two final guidances. One of the drafts, which focuses on the regulation of

combination device and cell tissue products. The guidance also notes what intended uses or specific attributes would result in a device with a regenerative therapy product being classified as a Class III device, and the factors to consider in determining whether a device may be labeled for use with a specific RMAT or class of RMATs.

devices used with regenerative medicine, implements a provision of the 21st Century Cures Act and strongly suggests that most of these products will be regulated via class II.

Read the full article here

BlueRock's Hei said this guidance will ease the burden of regulatory filings for these types of medicines.

The agency also issued a final guidance on Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): Minimal Manipulation and Homologous Use. It explains the criteria of minimal manipulation and homologous use and notes that over the next 36 months FDA will exercise enforcement discretion with respect to IND applications and BLA requirements for certain of these products.

Another draft guidance consists of questions and answers for tissue establishments and healthcare professionals on surgical procedures excluded from regulations for HCT/Ps.