February 15, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-D-6159: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Submitted via www.regulations.gov

Dear Sir/Madam:

Biocom is the largest, most experienced leader and advocate for California's life science sector, which includes biotechnology, pharmaceutical, medical device, genomics and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,000 members dedicated to improving health and quality of life, Biocom drives public policy initiatives to positively influence the state's life science community in the research, development, and delivery of innovative products.

In our mission of providing feedback and communication between regulators and industry, we are writing in response to the Food and Drug Administration's (FDA) request for comments on the draft guidance entitled "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" (the "Draft Guidance").

Biocom commends the agency on its efforts to develop a comprehensive regenerative medicine framework to spur innovation and access to potentially life-saving treatments while ensuring safety and efficacy. The release of this Draft Guidance has provided important information on the expedited programs available to sponsors of regenerative medicine products. Our comments, detailed further in the balance of this letter, focus on the following areas:

Definition of Regenerative Medicine

- Biocom recommends that the final guidance specifically state that "autologous" and "allogeneic" therapies are included in the definition of regenerative medicine therapy to eliminate any uncertainty.

RMAT Eligibility Criteria

- Biocom recommends that the final guidance provide greater clarity on the level of evidence required for RMAT designation and how it compares to breakthrough and fast track.
- FDA should clarify the impact of a sponsor of a regenerative advanced therapy obtaining fast track designation based on preliminary clinical evidence.
- Biocom believes that sponsors of regenerative medicine products should not be required to separately establish that the product is intended to treat a serious disease or condition each time it applies for a different designation.

Requirements for Preliminary Clinical Evidence

- FDA's final guidance should specify that a study with an appropriate historical control could satisfy the burden of preliminary clinical evidence required for RMAT designation even if that historical control was chosen post hoc.
- The final guidance should explain what is intended by the sentence in the Draft Guidance that reads, "it is essential that the preliminary clinical evidence be generated using the regenerative medicine therapy that is planned for clinical development, rather than a related product."
- Biocom urges FDA to provide greater clarity in the final guidance regarding the factors the agency will use in determining the sufficiency of preliminary clinical evidence. FDA should provide more detail in the final guidance on how these factors will be applied and, to the extent possible, illustrative examples.

Accelerated Approval

- Biocom recommends that the agency provide further clarification in the final guidance regarding how FDA intends to implement FD&C Act section 506(g)'s novel provisions relating to accelerated approval for products with RMAT designation.

Innovative Clinical Trial Design

- Biocom urges FDA to provide greater clarity in its final guidance on aspects of innovative clinical trial design discussed in the Draft Guidance.
- Biocom believes it would be beneficial to industry to provide guidance on a specific set of requirements for autologous regenerative medicine therapies that are more than minimally manipulated.

<u>Definition of Regenerative Medicine Therapies</u>

Biocom commends the agency on the clarification of the inclusion of gene therapies in the definition of regenerative medicine therapies. The definition in section 3033 of the 21st Century Cures Act left some doubt as to whether certain gene therapies would be included. FDA clarifies in the Draft Guidance that gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues, may meet the definition of a regenerative medicine therapy based on its interpretation of section 506(g)(8) of the FD&C Act. Biocom recommends that the definition also specifically state that it includes both "autologous" and "allogeneic" therapies to eliminate any uncertainty.

RMAT Eligibility Criteria

In its final guidance, FDA should provide clarity on the level of evidence required to obtain RMAT designation. For example, the Draft Guidance states that the level of evidence required to demonstrate eligibility for breakthrough therapy designation is higher than that for fast track designation. As pointed out in the Draft Guidance, breakthrough therapy designation requires that preliminary clinical evidence shows that the product may demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints. By contrast, fast track designation can be obtained through nonclinical (or clinical) data showing the potential of the product to address an unmet medical need.

The level of evidence required for RMAT designation appears to fall in-between the standards for breakthrough therapy designation and fast track designation. RMAT designation, like breakthrough therapy designation, can be obtained through preliminary clinical data, but it only requires that preliminary clinical evidence shows that the product has the potential to address an unmet medical need, rather than a substantial improvement over existing therapies on one more clinically significant endpoints.

We believe that the final guidance should indicate clearly that the level of evidence required for RMAT designation requires less evidence than breakthrough therapy designation but more than fast track designation. We recommend that the final guidance provide greater clarity on the level of evidence required for RMAT designation and how it compares to breakthrough and fast track to aid developers of regenerative advanced therapies in understanding the level of evidence required to obtain RMAT designation.

Relatedly, FDA should clarify the impact of a sponsor of a regenerative advanced therapy obtaining fast track designation based on preliminary clinical evidence. In that situation, although the sponsor applied for fast track designation, that sponsor would have satisfied the qualifying criteria for RMAT designation (preliminary clinical evidence demonstrating the ability to address an unmet medical need). FDA's final guidance should clarify whether, in such a situation, FDA would automatically grant RMAT designation to the product, or the sponsor would be required to apply for RMAT designation separately.

Additionally, FDA may consider not requiring that sponsors of regenerative medicine products separately establish that the product is intended to treat a serious disease or condition each time it applies for a different designation. If so, FDA may consider clarifying in the final guidance that once a sponsor has established in one request for designation that the product under development is intended to treat a serious disease, the sponsor will not be required to re-establish this point in subsequent requests for designation for the same indication.

Requirements for "Preliminary Clinical Evidence"

Biocom appreciates the discussion provided by the Draft Guidance of FDA's expectations for the types of clinical evidence that can constitute "preliminary clinical evidence" leading to RMAT designation. In some instances, however, we believe that the Draft Guidance may be impractical in the application of the standard.

For example, the Draft Guidance states that FDA "generally expect[s] that such evidence would be obtained from clinical investigations conducted to assess the effects of the therapy on a serious condition." The Draft Guidance goes on to state that although in many cases such evidence will be derived from prospective clinical trials with concurrent controls, in other cases the evidence may come from retrospective studies, case series, or studies with historical controls. In all cases, however, the Draft Guidance emphasizes that "it is essential that the preliminary clinical evidence be generated using the regenerative medicine therapy that is planned for clinical development, rather than a related product."

We believe that these statements raise at least two questions that would benefit from clarification in FDA's final guidance. First, by stating that the preliminary clinical evidence standard can be satisfied (in some cases) "from studies with appropriately chosen historical controls," the Draft Guidance appears to imply that such historical controls must be pre-specified in the corresponding study protocol. Biocom believes that such a requirement may hamper innovation and in some cases may simply be impractical. It is common for early-stage studies to lack a pre-specified control. This is particularly prevalent in the regenerative medicine space where products are frequently developed by small companies or medical clinics. In many cases, these sponsors may compare the data generated from these studies to appropriate historical controls only post hoc.

FDA's final guidance should specify that a study with an appropriate historical control could satisfy the burden of preliminary clinical evidence required for RMAT designation even if that historical control was chosen post hoc. Taking this approach would not necessarily mean that such a study would qualify as an adequate and well-controlled study for purposes of ultimate product approval. We believe, however, that such studies can satisfy the burden of preliminary clinical evidence for the sole purpose of RMAT designation without sacrificing patient safety or the rigor of FDA's standards for demonstrating efficacy. Such an approach would also foster innovation while recognizing the practical realities of small company development of regenerative medicine products.

Second, the final guidance should explain what is intended by the sentence in the Draft Guidance that reads, "it is essential that the preliminary clinical evidence be generated using the regenerative medicine therapy that is planned for clinical development, rather than a related product." Requiring that the preliminary clinical evidence used to justify RMAT designation be obtained from studies using the regenerative therapy planned for clinical development may have the potential to stifle innovation. Many regenerative advanced therapies are individualized such as autologous stem cells where the biological source is always different. Similarly, regenerative medicine products often evolve during the development process, as techniques are refined. Requiring that preliminary clinical evidence used to support RMAT designation come from the same product that is planned for clinical development could unnecessarily limit the development of potentially life-saving regenerative medicine products.

Therefore, we recommend that FDA consider a more flexible approach in its final guidance to potential sources of preliminary clinical evidence. At a minimum, the final guidance could provide a discussion on the differences in the regenerative medicine therapies used for clinical development, related products, the ultimate product developed, and what FDA considers to be an appropriate source for preliminary clinical evidence.

Finally, we urge FDA to provide greater clarity in the final guidance regarding the factors the agency will use in determining the sufficiency of preliminary clinical evidence. The factors listed in the Draft Guidance include, "the rigor of data collection; the nature of meaningfulness of the outcomes; the number of patients or subjects, and the number of sites, contributing to the data; and the severity,

rarity, or prevalence of the condition." FDA should provide more detail in the final guidance on how these factors will be applied and, to the extent possible, illustrative examples.

Accelerated Approval

Biocom recommends that the agency provide further clarification in the final guidance regarding how FDA intends to implement FD&C Act section 506(g)'s novel provisions relating to accelerated approval for products with RMAT designation.

For example, for most drugs, FD&C Act section 506(c) sets forth the bases upon which FDA may grant accelerated approval. These include:

a) Surrogate endpoints that are reasonably likely to predict clinical benefit; and

b) Clinical endpoints that can be measured earlier than irreversible morbidity or mortality, that are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit ("intermediate clinical endpoints").

For RMAT products, however, FD&C Act section 506(g)(6) provides the bases upon which FDA may grant accelerated approval. That provision appears to expand the bases available in the RMAT context. Specifically, FD&C Act section 506(g)(6)(b) specifies that for RMAT products, FDA may grant accelerated approval based on either:

(i) Surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or,

(ii) Reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate.

This statutory provision creates significant ambiguity regarding the pathways to accelerated approval for RMAT products. For example, does FDA view FD&C Act section 506(g)(6)(b)(ii) as creating a third and entirely separate potential type of endpoint upon which accelerated approval can be based? If so, how does FDA define this endpoint and what kinds of confirmatory studies would FDA anticipate being used to verify and describe the clinical benefit in this situation? If FDA does not view "reliance upon data obtained from a meaningful number of sites" as a separate and distinct endpoint upon which an RMAT product can base accelerated approval, how does FDA reconcile the fact that the statute clearly permits reliance on such data as an alternative to reliance upon a surrogate or intermediate endpoint? How would "reliance upon data obtained from a meaningful number of sites" differ from a traditional drug approval which, by definition, must rely upon data obtained from a meaningful number of sites?

The Draft Guidance does not help resolve these and other ambiguities as it only states that determination of whether the number of investigational sites relied upon by a sponsor is "meaningful" will be a BLA-review issue. Whether the number of clinical sites used to generate data is "meaningful" is a review issue for every BLA, whether submitted for accelerated approval or traditional approval, and whether an RMAT product or a monoclonal antibody. By adopting new FD&C Act section 506(g)(6)(b)(ii), we believe that Congress clearly intended to create a novel approach to accelerated approval for RMAT designated products in order to foster innovation and

regulatory flexibility. We urge FDA to provide greater dimension to this new pathway in its final guidance

Considerations in Clinical Trial Design

We urge FDA to provide greater clarity in its final guidance on aspects of innovative clinical trial design discussed in the Draft Guidance. For example, the Draft Guidance states that for regenerative medicine therapies for more common diseases, FDA may support an innovative approach wherein "multiple clinical sites participate in a multi-center trial with the intent of sharing the combined clinical trial data to support BLAs from each of the individual centers/institutions." The Draft Guidance then states that in such trials, "manufacturing would be performed at all clinical sites using a common manufacturing protocol and product quality testing specifications."

Biocom applauds FDA's efforts to foster innovative clinical trial designs and novel pathways to approval for regenerative medicine therapies. The potential approach highlighted above, however, raises several questions that should be addressed in FDA's final guidance. For example, would such a multi-center study be conducted under a single investigational new drug (IND) application or would each clinical site be required to open its own IND in anticipation of ultimately submitting its own biological license application (BLA)? If one common IND is used, who would be responsible for fulfilling the sponsor's obligations under good clinical practices? Who would FDA communicate with regarding issues that might arise during the study (e.g., a clinical hold)? Would each clinical site have a voice in resolving such matters or would FDA designate a single site as the "sponsor" for purposes of communication with FDA and decision-making? Which site or sites would ultimately have authority, as the sponsor of the study, to make such changes? We encourage FDA to address these and other ambiguities inherent in such a multi-center clinical trial intended to support each site filing their own BLA.

Finally, there is still no clear description of a path towards regenerative medicine outside a traditional clinical trial system to encourage this new type of treatment development, particularly for autologous medicine outside of minimum manipulation. Of interest is guidance on a specific set of requirements for autologous regenerative medicine therapies that are more than minimally manipulated. Biocom recommends that the IND requirements for autologous therapies be further specified including chemistry, manufacturing, and controls (CMC), preclinical, and clinical trial design, particularly for regenerative medicine derived from autologous pluripotent stem cells such as induced pluripotent stem cells (iPSC). It would also be beneficial to the industry if the FDA provides a set of parameters on how to use autologous cells to replace approved allogeneic therapies (US or EU).

Thank you again for the opportunity to provide these comments. We look forward to a continued dialogue with the FDA on the expedited programs available to sponsors of regenerative medicine therapies. If you have any questions about these comments, please contact Brittany Blocker, Manager of Regulatory Affairs at bblocker@biocom.org.

Sincerely,

Joe Panetta

President and CEO
Biocom