May 28, 2019

UPS EXPRESS MAIL

David Greene, MD, MBA, Chief Executive Officer
R3 Stem Cell, LLC
6042 East Brianna Road
Cave Creek, AZ 85331

Dear Dr. Greene:

The Office of Compliance and Biologics Quality in the Center for Biologics Evaluation and Research (CBER) of the United States Food and Drug Administration (FDA) has reviewed the website for R3 Stem Cell, LLC, available at www.r3stemcell.com (R3 Stem Cell website, or website), which offers "regenerative stem cell therapies" at affiliated centers or clinics throughout the United States.

R3 Stem Cell promotes these stem cell therapies for numerous diseases or conditions, such as dementia and Parkinson's disease, *see* https://r3stemcell.com/conditions/dementia/, and directs patients with amyotrophic lateral sclerosis (ALS), diabetes, kidney failure, Lyme disease, Parkinson's disease, and stroke to certain "R3 Stem Cell Centers of Excellence" for stem cell treatment. For example, the website states:

- "R3 Stem Cell is now offering stem cell therapy for ALS at several Centers of Excellence." *See* https://r3stemcell.com/conditions/als/#.

- "R3 Stem Cell offers stem cell therapy for both Type 1 and Type 2 Diabetes at specialized Centers of Excellence." *See* https://r3stemcell.com/conditions/diabetes/.

- "Stem cell therapy for kidney failure is treated at various R3 Stem Cell Centers of Excellence." *See* https://r3stemcell.com/conditions/kidney-failure/.

- "R3 Stem Cell offers stem cell therapy for Lyme Disease . . . at Centers of Excellence." *See* https://r3stemcell.com/conditions/ lyme-disease/.

- "R3 Stem Cell is now offering stem cell therapy for Parkinson's Disease at several Centers of Excellence." *See* https://r3stemcell.com/conditions/parkinsons-disease/.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

- "R3 Stem Cell is now offering stem cell therapy for stroke at several Centers of Excellence." *See* https://r3stemcell.com/conditions/stroke/.

In addition, your website lists a variety of "conditions treated at R3 Stem Cell Clinics," including, among numerous others: rheumatoid arthritis, spinal stenosis, and trigeminal neuralgia. *See* https://r3stemcell.com/faq/.

The above-referenced stem cell therapies appear to be human cell, tissue, or cellular or tissue-based products (HCT/Ps) as defined in 21 CFR 1271.3(d) that would be subject to regulation under 21 CFR Part 1271, issued under authority of section 361 of the Public Health Service Act (PHS Act) [42 U.S.C. 264].

HCT/Ps that do not meet all the criteria in 21 CFR 1271.10(a), and when no exception in 21 CFR 1271.15 applies, are not regulated solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271. Such products are regulated as drugs, devices, and/or biological products under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and/or the PHS Act, and are subject to additional regulation, including appropriate premarket review.

Based on a review of your website, it appears that R3 Stem Cell, LLC does not qualify for any exception in 21 CFR 1271.15 and the stem cell therapies offered by R3 Stem Cell, LLC are intended for nonhomologous uses and would be regulated as drugs as defined in section 201(g) of the FD&C Act [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. In order to lawfully market a drug that is also a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after a demonstration that the product is safe, pure, and potent. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug (IND) application in effect as specified by FDA regulations [21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312].

We note that your products are intended to treat a variety of serious or life-threatening diseases or conditions. Such unapproved uses raise potential significant safety concerns. Additionally, because the products are administered by various higher risk routes of administration, including IV, their use, if contaminated could cause a range of adverse events. We direct your attention to FDA's comprehensive regenerative medicine policy framework for HCT/Ps, which is intended to spur innovation and efficient access to safe and effective regenerative medicine products. The policy framework is outlined in a suite of four guidance documents available on FDA's website at https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm585218.htm.

Manufacturers and health care professionals who have any uncertainty regarding the regulatory status of their products are encouraged to contact FDA to obtain a recommendation or decision regarding the classification of an HCT/P. For more information in this regard, or to obtain further information about IND requirements for biological products, please see pages 23 and 24 of the guidance entitled, Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products:

Minimal Manipulation and Homologous Use at the link to FDA's webpage provided above.

This letter addresses certain issues regarding some of the products your website offers at affiliated centers or clinics and is not intended to be an all-inclusive review of those products. You and your firm are responsible for ensuring that all your products fully comply with the PHS and FD&C Acts and all applicable regulations. Any response to this letter should be sent to the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 10903 New Hampshire Avenue, Bldg. 71, Silver Spring, MD 20993. If you have any questions regarding this letter, please contact the Division of Case Management, CBER at (240) 402-9155. Please be advised that only written communications are considered official.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: David Greene, MD, MBA, Chief Executive Officer
R3 Stem Cell, LLC
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