U.S. FOOD & DRUG ADMINISTRATION

The Honorable Charles E. Grassley
Chairman
Committee on Finance
United States Senate
Washington, DC 20510

JUN 13 2019

Dear Chairman Grassley:

Thank you for your April 13, 2018, letter regarding US Stem Cell Clinic, LLC (USSC), as well as its listing of studies on *ClinicalTrials.gov*. We appreciate your interest in this important issue and welcome the opportunity to respond.

As you are aware, on August 24, 2017, the Food and Drug Administration (FDA) issued a warning letter[1] to USSC, which cited significant violations of current good manufacturing practice requirements and stated that the Stromal Vascular Fraction (SVF) Product manufactured by USSC, which is generally administered intravenously or intrathecally for a variety of diseases or conditions, is a drug and biological product being marketed without FDA approval. The letter also discussed how Kristin Comella, USSC's Chief Scientific Officer, had impaired FDA investigators' ability to conduct the inspection and reminded her that it is a prohibited act to refuse to permit entry or inspection as authorized by section 704 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. 374]. *See* 21 U.S.C. 331(f). Under section 501(j) of the FD&C Act [21 U.S.C. 351(j)], a drug is deemed to be adulterated when it has been manufactured, processed, packed, or held in any facility for which an owner, operator, or agent delays, denies, limits, or refuses an inspection.

FDA referred to the Department of Justice a civil enforcement action against US Stem Cell Inc., US Stem Cell Clinic LLC of Sunrise, Florida, and individual defendants, including Chief Scientific Officer Kristin Comella. The Department of Justice filed a civil complaint seeking a permanent injunction against those defendants on May 9, 2018.[2] The government moved for summary judgment in that case on March 11, 2019. On June 3, 2019, the United States District Court for the Southern District of Florida granted the government's motion for summary judgment.

As I'm sure you understand, FDA cannot confirm or deny the existence of any criminal actions related to this matter, should any such actions exist.

Regarding the listing of studies on *ClinicalTrials.gov*, the National Institutes of Health (NIH) maintains the *ClinicalTrials.gov* data bank. The information on *ClinicalTrials.gov* is provided by the sponsor or principal investigator of a clinical trial, who is responsible for ensuring that the

[1] The FDA Warning letter can be accessed at *https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm573187.htm.*
[2] Additional information can be found at the following website: *https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm607257.htm.*

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clinical trial is conducted in compliance with all applicable laws and regulations. Posting on *ClinicalTrials.gov* by the NIH does not reflect that the Federal government has evaluated or otherwise endorses a study. There are significant public health benefits to requiring the disclosure of information about clinical trials, including to prevent incomplete and biased reporting of individual trials, and to provide information about a more complete and unbiased set of trials. These benefits from clinical trial disclosure also help investigators fulfill an ethical obligation they have to clinical trial participants – to ensure that the findings from their participation in research will contribute to the expansion of knowledge pertaining to human health. *ClinicalTrials.gov* accepts information about biomedical or health-related studies in human subjects. Before a study record is posted on *ClinicalTrials.gov*, the following specific requirements must be met:

1. The data submitter must establish an account in the Protocol Registration and Results System (PRS)[3] and accept the PRS Terms and Conditions,[4] which include attestations to the accuracy of the responses;
2. The data submitter must provide all required study information, including (for registration) descriptive, recruitment, location and contact information, and administrative data, including whether the study has been approved by a human subjects protection review board;[5]
3. The submitted data must meet all automated validation rules to ensure that all required information has been provided;
4. The data submitter must approve the record for submission to *ClinicalTrials.gov* for processing;
5. The record undergoes manual quality control (QC) review[6] conducted by NIH's *ClinicalTrials.gov* staff following established criteria to identify apparent errors, deficiencies, or inconsistencies.

Before a study can be posted on *ClinicalTrials.gov* as "recruiting participants," the data submitter must indicate that the study either (1) was approved by a human subjects protection review board, (2) is exempt from such approval, or (3) is not required to obtain such approval (in accordance with applicable laws, regulations, or institutional policies for human subjects review). For a more in-depth look at this process, please see the PRS User's Guide, Section 2: Record Basics: Steps to Posting a Study Record on *ClinicalTrials.gov*.[7]

Research participant safety is of utmost importance to the Department of Health and Human Services. The *ClinicalTrials.gov* website currently includes information to help potential participants learn more about the potential risks and benefits of participating in a trial, and urges people to talk to their doctors about whether to join a study. NIH is exploring additional measures that could be taken to enhance understanding of what it means to be in a clinical

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[3] Protocol Registration and Results System (PRS): *https://register.clinicaltrials.gov.*
[4] See Section 11: Terms and Conditions of the PRS User's Guide: *https://prsinfo.clinicaltrials.gov/prs-users-guide.html.*
[5] See Data Element Definitions available here: *https://clinicaltrials.gov/ct2/manage-recs/resources#DataElement.*
[6] Protocol Review Criteria (*http://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf*) and Results Review Criteria (*http://prsinfo.clinicaltrials.gov/ResultsDetailedReviewItems.pdf*).
[7] *https://prsinfo.clinicaltrials.gov/prs-users-guide.html#recordbasics.*

research study and how to navigate *ClinicalTrials.gov*. NIH has also added more prominent disclaimers to the site to help ensure that users are aware that the listing of a study on the site does not reflect evaluation or endorsement of the trial by the Federal government.

Collectively, the steps described above aim to ensure that entries listed on *ClinicalTrials.gov* are, in fact, research studies. Required registration data elements are designed to elicit components of a research study, and the manual quality control process, which is designed to identify apparent errors, deficiences, and inconsistencies in the submitted information, helps ensure that the submitted data elements, including the study design, are consistent with that of a research study.

NIH provides extensive educational information at *ClinicalTrials.gov* to assist those who may be considering enrollment in a clinical trial. The "Learn About Clinical Studies" page, for example, contains information about what a clinical study is, reasons for conducting clinical studies and participating in clinical studies, including information about human subjects protections, the relationship of clinical studies to health care, and questions to consider before participating in a study.[8] NIH recognizes the challenge in communicating nuanced information to the public and continues to evaluate the resources made available on *ClinicalTrials.gov*. NIH is committed to continuing to improve these resources to help ensure people understand important issues to consider before participating in a clinical trial.

As noted, NIH has improved the prominence and readability of disclaimers on the *ClinicalTrials.gov* homepage and in individual study records. In 2017, NIH worked with the digital services consultancy of the General Service Administration (referred to as 18F) to evaluate several versions of a disclaimer using different content, placement, and formatting with actual *ClinicalTrials.gov* users representing various stakeholders. Based on the results of this review, NIH implemented on the homepage and on study record pages disclaimers that were found, through the evaluation process with 18F, to be most easily understood by users as conveying the message that listing a study on this site does not mean it has been evaluated or endorsed by the U.S. Federal Government. NIH continues to solicit feedback on these additions to the website.

Thank you again for your letter.

Sincerely,

Karas Gross
Associate Commissioner for
Legislative Affairs

[8] See Learn About Clinical Studies available here: *https://clinicaltrials.gov/ct2/about-studies/learn.*