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Comments Regarding Food and Drug Administration Enforcement of Regulations Applicable to Stem Cell and Regenerative Medicine Clinics that are Using/Administering Unapproved Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Presented at the Listening Session Convened by the Food and Drug Administration's Center for Biologics Evaluation and Research, April 13, 2021

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group. Public Citizen is a nonprofit, consumer advocacy organization founded 50 years ago. Since our founding, we have advocated more rigorous and more transparent Food and Drug Administration (FDA) oversight of drugs, biologics, and medical devices. I have no financial conflicts of interest.

I would like to thank the FDA for the opportunity to share Public Citizen's views regarding actions that the agency should take with respect to stem cell and regenerative medicine clinics once the agency's enforcement discretion period that was originally specified in the agency's November 2017 guidance, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*, ends on May 31, 2021.

The following are our responses to the four questions posed by the agency to participants in this listening session.

Question 1: What do you recommend that FDA do with regard to stem cell and regenerative medicine clinics that are using/administering HCT/Ps, including cellular products, that are not FDA-approved, when enforcement discretion ends in May 2021?

In order to protect patients and public health, the FDA after May 31, 2021, must take swift and aggressive enforcement actions against establishments — including self-identified stem cell and regenerative medicine clinics — engaged in the manufacturing or marketing of HCT/Ps that (1) do not meet all of the criteria for regulation solely under section 361 of the Public Health Service (PHS) Act and FDA regulations at 21 C.F.R. Part 1271 that are specified under agency regulations at 21 C.F.R. § 1271.10(a)[1] and (2) have not received FDA premarket review and

[1] The criteria under 21 C.F.R. 1271.10(a) are as follows: (1) The HCT/P is minimally manipulated; (2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent; (3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and (4) Either: (a) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (b) The HCT/P has a systemic

approval in accordance with applicable regulations for drugs, biological products, or devices under the Food, Drug, and Cosmetic Act or section 351 of the PHS Act (42 U.S.C. § 262) (hereafter referred to as illegal HCT/Ps). Such action to stop the manufacturing, marketing, and use of these unapproved, illegal products that have the potential to cause serious harm to patients but have not been proven to be effective and raise false hopes for patients is long overdue. Indeed, it has been more than five years since the FDA held its Part 15 hearing regarding the agency's HCT/P guidance, at which time it was obvious to the agency and others that hundreds of stem cell and regenerative medicine clinics around the country were manufacturing and marketing illegal HCT/Ps.

The FDA should use all available legal authorities and tools to take administrative, judicial, and criminal actions against stem cell and regenerative medicine clinics and other establishments that continue to engage in manufacturing or marketing of illegal HCT/Ps in the U.S. after May 31. These actions should include the following:

- On June 1, 2021, the FDA should issue a press release and hold a press conference announcing the end of the agency's enforcement discretion and plans to immediately initiate aggressive enforcement actions against establishments that continue to engage in the manufacturing or marketing of illegal HCT/Ps in the U.S.
- FDA leadership should seek additional appropriated funding from Congress to support significantly expanded enforcement activities targeting illegal HCT/Ps.
- Through robust internet searches and other means, The FDA should identify establishments that appear to be manufacturing or marketing illegal HCT/Ps. Most of these establishments seek patients through web-based advertising. A quick search by Public Citizen in the past week identified websites for several dozen stem cell and regenerative medicine clinics that appear to offer unapproved stem cell therapies using autologous stem cells obtained from adipose tissue or bone marrow to treat one or more of the following diseases: Alzheimer's disease, chronic back pain, chronic obstructive pulmonary disease, diabetes, erectile dysfunction, heart failure, multiple sclerosis, osteoarthritis, peripheral vascular disease, stroke, and traumatic brain injury, among others. Hopefully, the FDA already has created its own list of such establishments.
- As the agency has done recently regarding illegal dietary supplements,[2] illegal opioids,[3] and fraudulent COVID-19 treatments,[4] the FDA should send and post on its website

effect or is dependent upon the metabolic activity of living cells for its primary function, and: (i) Is for autologous use; (ii) Is for allogeneic use in a first-degree or second-degree blood relative; or (iii) Is for reproductive use.

[2] Food and Drug Administration. FDA sends warning letters to 10 companies for illegally selling dietary supplements claiming to treat depression and mental illness – Constituent update. February 19, 2021. https://www.fda.gov/food/cfsan-constituent-updates/fda-sends-warning-letters-10-companies-illegally-selling-dietary-supplements-claiming-treat. Accessed April 11, 2021.

[3] Food and Drug Administration. FDA warns website operators illegally selling opioids to consumers. September 10, 2020. https://www.fda.gov/news-events/press-announcements/fda-warns-website-operators-illegally-selling-opioids-consumers. Accessed April 11, 2021.

[4] Food and Drug Administration. Fraudulent coronavirus disease 2019 (COVID-19) products. April 8, 2021. https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products. Accessed April 11, 2021.

batches of warning letters to multiple establishments that appear to be manufacturing or marketing illegal HCT/Ps in the U.S. based on these establishments' web-based or other advertising. The agency should issue press releases announcing such actions. These warning letters should (a) declare these HCT/Ps to be adulterated and misbranded, (b) demand that these establishments immediately cease their manufacturing or marketing of the illegal HCT/Ps in the U.S, and (c) threaten additional legal actions if they fail to comply.

- For establishments that fail to cease their manufacturing or marketing of illegal HCT/Ps, the FDA, as appropriate, should seek injunctions against these establishments in federal court, impose monetary civil penalties, and, if necessary, pursue criminal prosecutions in collaboration with the Department of Justice (DOJ). The FDA and DOJ should consider forming a federal task force targeting such establishments.
- The FDA should require investigational new drug (IND) applications for any stem cell and regenerative medicine clinics or other establishments that claim to be manufacturing and using HCT/Ps under the guise of institutional review board-approved clinical trials. Until such INDs are submitted, these establishments should be directed to cease such clinical trials.
- The FDA should require pre-clinical testing before the administration of any HCT/Ps to humans in a clinical trial.
- The FDA should encourage state Attorneys General and state medical boards to take the actions described in our response to the next question.

Question 2: What should stakeholders other than FDA do with regard to stem cell and regenerative medicine clinics that are using/administering HCT/Ps, including cellular products, that are not FDA-approved, when ED ends in May 2021?

The Attorneys General of any states where stem cell and regenerative medicine clinics and other establishments that are engaged in the manufacturing or marketing of illegal HCT/Ps should pursue enforcement actions under any applicable state laws, such as those that prohibit fraud.

State medical boards should pursue disciplinary action, including the suspension or revocation of medical licensure, for any physicians practicing in their states who are involved in manufacturing, marketing, or administering illegal HCT/Ps.

Question3: What can be done to encourage your organization's stakeholders to do clinical research to investigate the safety and efficacy of HCT/Ps, including cellular products, that are not FDA-approved?

Our organization does not have stakeholders that engage in clinical research investigating the safety and efficacy of HCT/Ps that are not FDA-approved.

Question 4: What can be done to inform patients/health professionals about the risks and unproven benefits of HCT/Ps, including cellular products, that are not FDA-approved?

The FDA should pursue a multi-faceted public education campaign to inform patients and health care professionals about the known risks of and lack of evidence of effectiveness for illegal HCT/Ps. The campaign should highlight specific examples of the harms that may result from such unapproved products, including:

- Administration site reactions
- Transmission of infections
- The ability of cells to move from placement sites and change into inappropriate cell types or multiply
- The growth of tumors

Again, thank the FDA for the opportunity to present our views on these urgent public health matter.