

ONE HUNDRED SIXTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
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July 25, 2019

Norman E. Sharpless, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Dear Acting Commissioner Sharpless:

We write to you today about concerns arising from the slower than expected progress of manufacturers and providers of marketed treatments containing stem cell products to come into compliance with premarket approval requirements. The Food and Drug Administration (FDA) recently announced that it has sent letters to 20 manufacturers and providers who may be offering unapproved stem cell products.^{1,2}

As you know, including these letters, the agency has sent 45 communications to manufacturers and providers on this topic. The FDA has also filed two lawsuits against clinics in California and Florida over the last year.³ While the court case is pending in California, a limited permanent injunction was issued against the Florida clinic's treatment just last month.⁴ Beyond FDA's actions, in April, the New York Attorney General announced a lawsuit against a stem cell clinic, alleging that the clinic employed misleading claims and engaged in deceptive

¹ Food and Drug Administration (FDA), *Warning Letter to Cord for Life, Inc.*, (March 29, 2019) (www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm635078.htm).

² FDA, *Letter Regarding Stem Cell Products*, (December 20, 2018) (www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/UCM628912.pdf).

³ New York Times, *Judge Halts Treatments at Florida Stem Cell Clinic* (June 25, 2019) (www.nytimes.com/2019/06/25/health/stem-cells-fda-injunction.html).

⁴ *Id.*

acts or practices to attract business.⁵ We appreciate the actions taken by FDA, but this pattern of unsafe and unproven therapies remains deeply concerning. Such treatments not only pose public health risks for patients, but also harm the future promise held by the development of stem cell therapy as a field.

The 21st Century Cures Act, which was signed into law by President Obama in December 2016, directed the FDA to provide a predictable regulatory program through which regenerative therapies, including stem cell therapies, could be developed and approved.⁶ The Regenerative Medicine Advanced Therapy (RMAT) designation program provides a clear incentive for developers of stem cell therapies to seek agency input early in their development process, which will facilitate expedited agency review, and the agency's guidance documents provide a clear process outlining the steps manufacturers must take in order to comply with the law. One guidance in particular—"Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use"⁷—clarified that the agency would be exercising enforcement discretion for 36 months under limited conditions while manufacturers come into compliance. With this added clarity from FDA about the premarket approval process and its quick work to clarify its expedited review program, it is difficult to understand why the industry has made only "modest progress"⁸ coming into compliance during the first half of this three-year period of enforcement discretion.

The slow pace of compliance is particularly concerning given the high stakes for patients. For example, many of these unproven therapies are being provided directly to patients outside of controlled clinical studies resulting in numerous serious adverse events, including infection, hospitalization, and permanent blindness.^{9,10,11} Furthermore, in the two complaints FDA has filed

⁵ Complaint, Attorney General of the State of New York v. Image Plastic Surgery, (April 3, 2019) (ag.ny.gov/sites/default/files/park_ave_stem_cell_clinic_complaint.pdf).

⁶ 21st Century Cures Act, H.R. 34, 114th Cong. (2016) (docs.house.gov/billsthisweek/20161128/CPRT-114-HPRT-RU00-SAHR34.pdf).

⁷ FDA, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use* (2017) (www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf).

⁸ FDA, *Statement by FDA Commissioner Scott Gottlieb, M.D., and Biologics Center Director Peter Marks, M.D., Ph.D.* (2019) (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635165.htm).

⁹ Complaint, United States of America v. California Stem Cell Treatment Center, Inc. (May 9, 2018) (www.isscr.org/docs/default-source/policy-documents/califcase5-10-18.pdf?sfvrsn=2).

¹⁰ *Id.*

¹¹ Washington Post, *This clinic's experimental stem cell treatment blinded patients. Years later, the government is still trying to stop it* (April 3, 2019).

against companies, the agency asserted that the clinics represented that their products are not subject to FDA review.¹² In fact, it seems that FDA became aware of adverse events associated with these therapies, at least in part, as a result of inspections conducted at the facilities where they were administered. The adverse events that have been published in formal clinical studies or listed in FDA's first two cases represent only the known adverse events. As FDA leadership has acknowledged, such adverse events may be more common than has been reported because reporting requirements have not been understood by developers to apply outside of clinical investigations.¹³ These adverse events highlight the need to study the safety and efficacy of stem cell therapies in a traditional clinical trial setting.¹⁴

When providers offer harmful, unproven stem cell therapies outside of the clinical setting, they create confusion among patients and undermine public confidence in treatments that have been proven to be safe and effective through well-designed clinical trials.¹⁵ If we are to realize the potential clinical benefits of stem cell therapies, it is crucial that developers focus their efforts on the use of traditional developmental pathways that yield definitive results rather than promoting products with "dubious clinical efficacy and possible risks."¹⁶

Equally crucial is the agency's continued vigilance of this burgeoning market. While FDA's efforts to remove violative products from the market are encouraging, we are very concerned about the proliferation of these unproven therapies throughout the United States. The advertising strategies some of these clinics employ to attract some of the most vulnerable patients are particularly alarming. Some have advertised stem cell treatments to desperate patients with the most serious untreated illnesses, such as spinal injuries, Parkinson's disease, and multiple sclerosis.¹⁷ Some clinics have misled patients into believing that the therapies they offer are FDA approved or that they are being offered as part of an FDA-sanctioned clinical trial.¹⁸ Even basic claims about this body of science—such as the claim that

(www.washingtonpost.com/national/health-science/this-clinics-experimental-stem-cell-treatment-blinded-patients-four-years-later-the-government-is-still-trying-to-shut-it-down/2019/04/03/432d6d04-ff2f-11e8-83c0-b06139e540e5_story.html?noredirect=on&utm_term=.070ea46af283)

¹² See note 9.

¹³ The New England Journal of Medicine, *Clarifying Stem-Cell Therapy's Benefits and Risks*, (March 16, 2019) (www.nejm.org/doi/full/10.1056/NEJMp1613723).

¹⁴ *Id.*

¹⁵ The New England Journal of Medicine, *Balancing Safety and Innovation for Cell-Based Regenerative Medicine*, (March 8, 2018) (www.nejm.org/doi/full/10.1056/NEJMs1715626).

¹⁶ *Id.*

¹⁷ See note 9.

¹⁸ See note 3.

these stem cells can “differentiate appropriately on the basis of the environment in which they are introduced”—have been shown to be inaccurate.¹⁹

As we approach the halfway point in this period of FDA enforcement discretion, we want to register our concerns about the proliferation of unproven stem cell therapies on the market and our desires to ensure that the agency is doing everything in its power to protect patients. We would like to better understand the FDA’s current strategy for monitoring the market and bringing these therapies into compliance. We would also like to understand the agency’s plans to implement a long-term enforcement strategy once this period comes to an end in November 2020.

Given this, we request that you provide a response to the following questions no later than August 15, 2019:

1. How is the agency’s current work on regenerative medicine therapies, including stem cells, resourced? Approximately how many requests has FDA received for INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER products) meetings prior to development of a stem cell therapy? How many of the potential sponsors that requested a meeting subsequently submitted an application? Of those applications that resulted from such an informational meeting, how many have requested an RMAT designation?
2. An article in the New England Journal of Medicine authored by Drs. Marks and Gottlieb²⁰ acknowledged the importance of providing tools that will encourage individuals or small groups of physicians to develop these products, such as a common manufacturing and clinical trial protocols. How many products is FDA aware of in the pipeline that are utilizing this approach to development? Have any such applications received RMAT designation? Have any applications using this approach received approval? Will the agency provide resources to explain how these tools could be best utilized by developers or to account for the number of products being developed under this approach?
3. Given the current development environment for stem cell therapies, are there strategies other government entities should be considering in order to engage with legitimate researchers early on in their process and spur the use of the traditional development pathways? Is FDA considering other strategies to encourage developers to engage with the agency early on?
4. How many agency officials are working to monitor adverse event reporting and respond to safety signals related to stem cell therapies? What level of staffing and funding has the FDA determined is needed to adequately monitor adverse event reporting and respond to

¹⁹ See note 12.

²⁰ See note 12.

safety signals related to stem cell therapies? Would additional resources help the agency to conduct a more rigorous survey of the market? Will additional resources be required when the period of enforcement discretion ends in November 2020?

5. As you prepare for November 2020, and the planned end to FDA's policy of enforcement discretion, how will you communicate the transition to enforcement to non-compliant stem cell clinics? How will you announce planned changes to enforcement policies?
6. How is FDA coordinating with other state and federal agencies? Is the agency coordinating with state medical boards? If not, would the agency consider coordinating its enforcement work with state medical boards or, at the very least, providing its compliance letters to such medical boards, which could revoke the licenses of physicians that perform these procedures?

Thank you for your prompt attention to this important matter. Should you have any questions, or should you want to discuss compliance with this request, please contact Kimberlee Trzeciak or Megan Howard with the Energy and Commerce Committee Majority staff at 202-225-5056 or Kristin Seum with the Energy and Commerce Committee Minority staff at 202-225-3641.

Sincerely,



Frank Pallone, Jr.
Chairman



Greg Walden
Ranking Member



Diana DeGette
Chair
Subcommittee on Oversight
and Investigations



Fred Upton
Ranking Member
Subcommittee on Energy