Update on FDA’s Comprehensive Regenerative Medicine Framework: Looming November 2020 Deadline Preceded by a Flurry of Letters from CBER and a New JAMA Editorial

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As we discussed in our last update on the Food and Drug Administration’s Comprehensive Regenerative Medicine Policy Framework back in December 2019 (during the much simpler, pre-COVID-19 world), this coming November will conclude the three-year period of enforcement discretion announced by the agency when it first articulated the policies and goals of this “comprehensive framework.” In particular, under the dual-track program announced in 2017, the Food and Drug Administration (FDA) has been focused on: (1) clarifying the regulatory criteria for product marketing through guidance and providing support to legitimate product...
developers through formal and informal interactions; and (2) removing unapproved, unproven, and potentially unsafe products from the U.S. market.

None of the COVID-19-related operational updates provided by the FDA generally or by the Center for Biologics Evaluation and Research (CBER) in recent months has suggested that the November 2020 deadline will be extended or otherwise altered as a result of the ongoing public health emergency, even as certain other enforcement discretion policies have been put into place. Additionally, a recent editorial published by agency leadership and a noticeable increase in Warning/Untitled Letters to persons offering unapproved cellular therapy products, taken together, strongly suggest that folks in this industry that are currently operating outside of the applicable regulatory framework should not expect to be given any additional time to come into compliance.

June 2020 JAMA Editorial – Strong Language and No Sign of a Deadline Extension

Multiple statements on the topic of regenerative medicine have been issued by the governing FDA Commissioner as well as CBER Director Peter Marks over the past several years, which indicates how important this area is to the agency’s broader public health priorities at the start of the 21st century. The most recent salvo from agency leadership came in the form of an editorial published online by JAMA on June 17, 2020, authored by Dr. Marks and Commissioner Stephen Hahn, who has been in his new job for about six months. Their editorial includes some of the strongest language we have seen to date on the topic of unapproved regenerative medicine products. For example, Dr. Marks and Dr. Hahn state that “[d]espite assertions by some individuals to the contrary, these products, whether autologous or allogeneic, are not inherently safe and may be associated with serious adverse consequences.” They assert that “[t]he increasing number of adverse events being reported following the widespread use of unapproved regenerative medicine therapies at hundreds of clinics across the country make it necessary for the FDA to act to prevent harm to individuals receiving them.”

Drs. Marks and Hahn briefly highlight some of the enforcement that the agency has undertaken in this space since 2017 and ask for engagement from “both clinicians and patients to help to ensure that instead of remaining unintentionally or intentionally hidden, potentially harmful unapproved regenerative medicine therapies are identified and removed from the market.” They then provide basic guidelines for patients and caregivers to use when assessing whether a cellular therapy product is being offered in compliance with applicable laws and FDA regulations. Specifically, they recommend the following key considerations for anyone considering treatment with a cellular product:

- Whether the product is FDA-approved or whether an Investigational New Drug (IND) application for the product is on file with the agency;

- Whether the patient is being asked to provide written informed consent to participate in a clinical trial under that IND and in accordance with institutional review board requirements;
Whether the patient is being asked to pay for either the unapproved product or to participate in the clinical trial;

Whether the patient is being encouraged to report potential adverse events and whether the health care provider clearly explains the methods for doing so; and

Whether patients enrolled in the clinical trial receive a summary of results after the trial is completed.

Nothing in this newly-published editorial suggests that FDA/CBER will be taking its proverbial foot off the pedal to slow down its efforts towards further oversight of the private stem cell clinic industry after November 2020. To the contrary, the piece could represent one of the last informal “warnings” those businesses get from the agency before they receive a customized Warning or Untitled Letter or become subject to whatever increased enforcement activity the federal government initiates in this area in 2021 and beyond.

Relatively Large Number of Warning Letters Sent Since January 2020

We previously noted that FDA/CBER appeared to have increased the pace of issuing Warning and Untitled Letters to sellers of unapproved stem cell products during the second half of 2019, with many of those letters involving companies that processed and marketed unapproved umbilical cord blood-derived cellular products. We also reported that the agency had issued a “Public Safety Notification on Exosome Products” on December 6, 2019, informing the public of multiple reports of serious adverse events experienced by patients in Nebraska who were treated with unapproved products marketed as containing exosomes. That safety alert also described the unscrupulous conduct of sellers of such products in forceful and direct language, similar to the language used by Dr. Marks and Commissioner Hahn in this month’s editorial piece.

Over the first half of this year, as we get yet closer to the November 2020 deadline for stem cell clinics and medical practitioners to come into compliance with federal law, there has been a more noticeable increase in the Warning/Untitled Letters issues regarding the marketing of unapproved products that put patients at risk. These include at least nine Untitled Letters issued since January 2020 (which can each be accessed from this CBER webpage) and at least two Warning Letters, one from March and one from June. The Warning Letters in particular include charges that the firms in question were violating current good manufacturing practices (CGMPs) and current good tissue practices (CGTPs) for human cells and tissue products, putting patient safety at risk.

Interestingly, the most recent FDA Warning Letter issued on June 4, 2020 not only cites the recipient for marketing unapproved stem cell products and an unapproved exosome product, but it also states that the unapproved exosome product was being marketed for the treatment and prevention of COVID-19 – something the June 17 Marks/Hahn JAMA editorial alluded to generally as well. Given that there are currently no FDA-approved products to prevent or treat COVID-19, any such claims will automatically heighten the enforcement risk to a company or physician engaged
In the sale of products for those intended uses.

In addition to the work being done by FDA, moreover, the Federal Trade Commission (FTC) has also been monitoring the commercial marketplace closely and taking various actions to protect consumers from fraudulent COVID-19 products, including a few marketed by stem cell clinics. So far this month, FTC announced on June 4, 2020 that it had issued a 35 warning letters and an additional 30 warning letters on June 18, 2020. The first batch of these FTC warning letters notably included one to a stem cell clinic that, among other things, had claimed that “stem cells can be administered intravenously and by inhalation through a nebulizer to treat lung damage caused by COVID-19” without scientific evidence to support the efficacy claim, while the second batch included two letters addressed to marketers of stem cell products.

FDA and the FTC coordinate quite closely on consumer protection matters that implicate both agencies’ primary missions, as is apparent from the large number of COVID-19 Warning Letters that have been jointly issued by the two agencies since March 2020. So they may very well be coordinating more actively now on the monitoring of stem cell clinics and individual physicians offering unapproved cellular therapies to the general public, as the focus shifts to the next phase of the Comprehensive Regenerative Medicine Policy Framework. The next five or six months should offer everyone more insight into what the enforcement landscape is likely to evolve into once the FDA’s enforcement discretion period ends in November. As always, we’ll keep our readers apprised of any notable developments.

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