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June FDA memo reaffirms guidelines from 2017 in regard to human cell, tissue product use

Clinicians need to be aware of the contents of the June 3 memo from the FDA regarding use of human cell and tissue products and must realize that the guidance issued Nov. 15, 2017, has not changed, according to a regulatory consultant.

Scott Bruder, MD, PhD, who works with companies to help get new drugs, devices, biologics and combination products through the FDA approval process, discussed the June 3 memo, "Important Patient and Consumer Information About Regenerative Medicine Therapies." He told Healio Orthopedics the purpose of the memo, which was addressed to patients and consumers, was to mark the official end on May 31, 2021, of the period of enforcement discretion for human cell and tissue orthobiologics that began with the "comprehensive policy framework for the development and oversight of regenerative medicine products, including novel cellular therapies" guidance released in November 2017 by then FDA Commissioner Scott Gottlieb, MD.

No new or updated rules were included in the June 3 memo, Bruder said.


Scott Bruder

According to the June 3 memo, "[Unapproved] products require FDA licensure/approval to be marketed to consumers. Before approval, these products require FDA oversight in a clinical trial. These unapproved products whether recovered from your own body or another person's body, include stem cells, stromal vascular fraction (fat-derived cells), umbilical cord blood and/or cord blood stem cells, amniotic fluid, Wharton's jelly, ortho-biologics, and exosomes. FDA has received reports of blindness, tumor formation, infections, and more, detailed below, due to the use of these unapproved products."

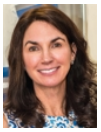
Disallowed use

Some human cell and tissue products (HCT/Ps) could not be legally sold before May 31, and still cannot be sold, according to Bruder, who serves on the American Academy of Orthopaedic Surgeons Basic Science/Education Committee and is co-editor of an upcoming book titled 'Orthobiologics: Scientific and Clinical Solutions for Orthopaedic Surgeons'.

"No stem cell products are approved for orthopedic conditions," he said.

Regarding certain other products, orthopedic surgeon **Joanne Halbrecht, MD, FAAOS,** told Healio Orthopedics, "If you look at the actual guidance, you'll see that it's never been legal. Doctors need to know about the regulations. They need to educate themselves, as well, regarding safety and efficacy."

The caveat to this is when these products are used by a physician in an appropriately registered clinical trial as part of the FDA-approval process, and the trial participants do not pay to be treated with the products within the confines of the trial, Bruder said.


Joanne Halbrecht

When the initial guidance was announced, the end date of the discretionary period of enforcement on certain biologics was November of 2020, "exactly 36 months from the 2017 announcement. But, as a result of COVID and some of the challenges that FDA perceived sponsors were having getting trials moving forward, they elected to give a 6-month extension," Bruder said. Hence the June 3 memo, reminding people of the end of the discretionary period on May 31, 2021.

Bruder, who has given seminars, lectures and webinars on this topic since before the November 2017 guidance, said, "I and others have been providing presentations at various specialty meetings and in publications, and the agency has been making it clear. So, anybody who's working in this space should not be surprised at the June 3 memo."

At the first recent chance he had to do so in person, Bruder spoke about the June 3 FDA memo at the Biologic Association Annual Summit held during the American Orthopaedic Society for Sports Medicine and Arthroscopy

Association of North America Combined Annual Meeting held July 7-11, in Nashville, Tennessee.

"As I discussed at the Nashville event, there's nothing new in there. It's simply a reiteration of the 2017 rules," Bruder said.

He presented on this topic at the Vail Scientific Summit held Aug. 19-22, in Vail, Colorado, and will do so, as well, at the AAOS Annual Meeting in San Diego during an instructional course lecture on Sept. 2, moderated by Halbrecht.

Halbrecht said she recently spoke on this topic at the MSK Ultrasound and Orthobiologics Course held July 29-31, in Las Vegas, where she said she told attendees, "Basically, you cannot use allogeneic products from the list described in the FDA memo of June 3. You're safe using FDA-cleared devices to prepare autologous HCT/Ps, but when the HCT/P is used in an off-label indication you need to justify that clinical use to the patient and obtain appropriate consent."

Discretionary enforcement period

What came to an end on May 31 was the period of FDA enforcement discretion, during which time FDA was focusing their attention on those companies and physicians selling unapproved HCT/Ps associated with the highest risk profile, Bruder said.

"That means FDA was taking a risk-based approach to enforcement actions such as issuing Warning or Untitled Letters. During that period, it didn't mean everybody got a free pass. It meant the agency was watching and would pursue those who appear to be participating in activities of highest risk," Bruder said.

Bruder explained that during the time from November 2017 to May 31, 2021, the FDA cited companies offering stem cell products that were being injected into the eye or spinal cord, for example, because these were considered high-risk procedures.

By comparison, the injection of micronized amniotic membrane into the knee to manage osteoarthritis, though still an unapproved product, was not the subject of any significant enforcement activity by FDA, he said.

"They did not aggressively go after companies like MiMedx Group who were selling such products, even though the guidance said you need a [biologic license approval] BLA for that. Companies like that were waiting to see, 'Well, after May 31, should I continue to market this? Is the agency going to give me a free pass while I pursue an appropriate regulatory approval?' And the answer to that is no," Bruder said. Currently, MiMedx has several FDA-registered studies ongoing to address the regulatory requirements for their micronized amnion products, Bruder noted.

According to the FDA memo, "Regenerative medicine therapies have not been approved for the treatment of any orthopedic condition, such as osteoarthritis, tendonitis, disc disease, tennis elbow, back pain, hip pain, knee pain, neck pain, or shoulder pain."

Bruder said, "An important principle is that physicians understand that they may use any product that has a proper legal basis for commercial availability however they choose, based on their clinical judgment, the same way they prescribe pharmaceuticals in an off-label way; that's called the practice of medicine. What they may not do is sell or deliver products to patients that have no basis for legal commercialization. And there are many out there because of the bad behavior of certain companies that continue to sell their adulterated or misbranded products in the absence of an appropriate regulatory approval. There's a list of such products in that June 3 memo, including amniotic fluid, Wharton's jelly, micronized amniotic membrane or anything that's called a 'stem cell'. There are no stem cell approved products for orthopedics. Period. So don't market, promote or advertise that you're doing anything with stem cells for treatment of your patients because that's regarded as false advertising by the [Federal Trade Commission] FTC and serves as a beacon for the FDA to contact you, and not with good news. FDA says they have sent out approximately 400 enforcement letters to sponsors and physicians in the last 3 years," Bruder said.

According to Halbrecht, "If you're going to use biologics ethically and legally and be able to use and market this appropriately to your patients, you need to be on top of FDA and FTC regulations, as well as the published research. Examples exist where clinics and physicians have incurred multimillion dollar fines and loss of medical licensure for violating these regulations."

She suggested that physicians list some relevant studies at their website and have patients read those studies and then decide for themselves if they want to pursue treatment.

The way physicians use and market HCT/Ps and orthobiologics needs to be backed by science and be ethical, Halbrecht said.

"The best way we can help patients and make them feel better is to offer them products that are safe and efficacious and be able to feel good about how we're marketing it to them. We want to be on top of technology. Biologics is the future of orthopedic medicine. It's great to offer our patients something that's an alternative to a surgical procedure," Halbrecht said.

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