AAOS
American Academy of Orthopaedic Surgeons
American Association of Orthopaedic Surgeons

November 15, 2021

Janet Woodcock, MD
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Acting Commissioner Woodcock,

On behalf of the 34,000 orthopaedic surgeons and residents represented by the American Association of Orthopaedic Surgeons (AAOS) and the undersigned organizations, we are pleased to share our positions on the current needs in biological product regulation. The AAOS works closely with legislators on Capitol Hill and regulators at the Department of Health and Human Services (HHS), including at the Centers for Medicare & Medicaid Services (CMS), and the Food and Drug Administration (FDA). In addition to commenting on annual payment rules and collaborating across coalitions to introduce physician and patient-benefiting legislation, AAOS partners with government leaders in health policy to improve safety for musculoskeletal patients. From providing clinical expertise to the Network of Experts Program and advisory committee public meetings to participating in stakeholder coalitions like the Orthopaedic Alliance Roundtable, the AAOS has collaborated closely with the FDA over the years. We look forward to continuing this partnership with the FDA under your leadership and focusing on the following priorities:

Continued Enforcement of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps) Regulations

In April of this year, the FDA announced it would definitively end compliance and enforcement discretion with respect to the investigational new drug and premarket approval requirements for certain HCT/Ps on May 31, 2021. The AAOS applauds this decision and encourages the FDA to begin active enforcement for those entities in non-compliance. As highlighted by Golish et al. (2021), "designing and executing high quality studies is complex, expensive, and risky; without any regulatory requirement to do so, many vendors pursue a commercially oriented approach with limited clinical evidence".[1] However, the FDA acknowledges that:

> "Despite all of the FDA's efforts to engage industry, there continues to be broad marketing of these unapproved products for the treatment or cure of a wide range of diseases or medical conditions. Many of these unapproved products appear to be HCT/Ps that are regulated as drugs, devices and/or biological products subject to premarket approval requirements. The wide extent of the marketing of such unapproved products is evidenced by their inappropriate advertisement in various media and by the number of consumer complaints about them submitted to the FDA."[2]

[1] Golish, S.R., Pezold, R., & Jevsevar, D. S. (2021, August 24). FDA Ends Enforcement Discretion on Biologics and Regenerative Products. *AAOS Now*. https://www.aaos.org/aaosnow/2021/aug/research/research01/
[2] US Food and Drug Administration. (2021, April 21). Advancing the Development of Safe and Effective Regenerative Medicine Products. *FDA Voices*. https://www.fda.gov/news-events/fda-voices/advancing-development-safe-and-effective-regenerative-medicine-products

Non-compliant vendors and providers undercut the efforts of those who are acting in good faith. As illustrated by Peter Marks, MD, PhD, the Director of the Center for Biologics Evaluation and Research (CBER), since December 2019 the agency issued more than 350 letters to manufacturers, clinics, and healthcare providers that may have been offering unapproved regenerative medicine products.[3] Therefore, we can presume that some vendors and providers will continue to try to bend the rules, requiring active enforcement. These vendors have had a four-year grace period to comply and can no longer be allowed to put patients at risk with unapproved products and procedures. In the short time since the end of enforcement discretion, CBER has issued seven Untitled Letters for products that appear to be derived from HCT/Ps as defined in 21 CFR 1271.3(d) that would be subject to regulation under 21 CFR Part 1271[4]. The AAOS is encouraged by the steps taken by the FDA to advance the development of safe and effective regenerative medicine products and asks that the agency continue active enforcement as it relates to regulation of HCT/Ps.

Clarification on the Regulatory Status of Concentrated Bone Marrow Aspirate (BMAC) and Cellular Bone Matrices (CBM)

An area of emerging interest for HCT/P therapeutic applications, is Concentrated Bone Marrow Aspirate, commonly referred to as BMAC. However, because the centrifuge machines used for this treatment were essentially a platelet-rich plasma (PRP) centrifuge originally regulated as a 510(k) Class II device, some BMAC machines have historical labels with no indications associated with the labels, while modern PRP labels have a narrow indication for "improving handling of bone graft", but do not include BMAC. Clarifying which centrifuge devices are on label for BMAC and what the indication for BMAC is critical. Currently, these devices are being marketed for a plethora of regenerative applications, some with more potential for adverse events than PRP itself.

Additionally, the field would benefit from guidance addressing the regulatory status of cellular bone matrices (CBM). Although vendors have been less aggressive in rhetoric around "stem cells," products which claim supraphysiologic concentrations, but still minimally manipulated and homologous (and therefore, eligible for regulation exemption under section 361) remains unclear.

Differentiating Between Legitimate Use and Investigational Use of Biologic Therapies

There is considerable promise to future application of emergent biologic therapies, and additional research is necessary to identify and test appropriate applications. While many researchers adhere to the gold standards of evidence-based medicine, there are still clinics running "trials," which are falsely advertised as effective or regenerative, with no intention of publishing results. This unethical practice erodes trust in those attempting to study and develop these technologies with appropriate scientific rigor. To protect patient safety, medical providers must be armed with clear guidance on differentiating between legitimate use versus investigational use of biologic therapies and patients must be equipped to identify those trying to profiteer. The AAOS strongly encourages the FDA to develop more resources for patients and

[3] US Food and Drug Administration. (2021, April 21). Advancing the Development of Safe and Effective Regenerative Medicine Products. *FDA Voices*. https://www.fda.gov/news-events/fda-voices/advancing-development-safe-and-effective-regenerative-medicine-products

[4] US Food and Drug Administration. (2021, September 20). *BIMO/Team Biologics/Internet Surveillance/Other*. https://www.fda.gov/vaccines-blood-biologics/enforcement-actions-cber/bimoteam-biologicsinternet-surveillanceother

providers that distinguish the legitimate, approved uses of biological therapies and act against entities not acting in good faith. Creation of these resources should include feedback from patients and providers to ensure accessibility, applicability, and that resources are made widely available to the public.

Continued and Enhanced Use of Real-World Evidence (RWE)

The 21st Century Cures Act of 2016 directed the FDA to explore the potential for use of real-world evidence (RWE) in regulatory decision making and since that time the Agency has created a framework for its Real-World Evidence Program and issued a draft guidance on *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics*. The use of RWE to monitor and identify trends and outcomes for both biologic treatments and devices benefits all involved, allowing the FDA to rely on larger and more robust datasets to supplement approval processes. It allows for greater confidence in the real-world and longer-term outcomes associated with treatments beyond the scope of randomized controlled trials. The AAOS supports continued and enhanced use of RWE by the FDA.

Additionally, we call on the FDA to collaborate with the Centers for Medicare & Medicaid Services (CMS) when possible to bridge the gap between market approval and Medicare coverage of innovative drugs, devices, and biological products. Though CMS has proposed repeal of the Medicare Coverage of Innovative Technology (MCIT) and Definition of 'Reasonable and Necessary' Final Rule, the AAOS supports the intent of the MCIT Pathway and believes a similar policy, with the addition of criteria for safety and efficacy in the Medicare population, should be developed for drugs, diagnostics, and/or biologics subject to breakthrough or expedited FDA approval mechanisms.

Thank you for your time and attention to the health policy priorities of the American Association of Orthopaedic Surgeons (AAOS). The AAOS looks forward to working closely with the FDA on further improving the health care system and enhancing the care of musculoskeletal patients in the United States. Should you have any questions or would like to work together in pursuit of our shared goals, please do not hesitate to contact Shreyasi Deb, PhD, MBA, AAOS Office of Government Relations at deb@aaos.org.

Sincerely,

American Orthopaedic Society for Sports Medicine

Arthroscopy Association of North America

Biologic Association

International Cartilage Regeneration & Joint Preservation Society