Editorial Commentary: Food and Drug Administration Regulation of Biologics in Orthopaedics: Am I the Only One Around Here Who Gives a Flip About the Rules?!?!

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Abstract: As orthobiologics have appeared and stayed a part of our clinical practices, at times it seems that we (orthopaedic surgeons) have not focused appropriate attention and/or interest on regulation. However, regulation has focused on us, as the Food and Drug Administration (FDA) has made it clear. Safety and efficacy are top priorities of the FDA and should be ours too. The FDA has transmitted their communications to industry and to clinicians; we are responsible for understanding their regulations and the FDA definitions of relevant terms, including "minimal manipulation" and "homologous" use. Finally, FDA "clearance" does not mean safe or efficacious, nor compliant with other federal regulations.

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Any *Big Lebowski* Fans out there? As orthobiologics have appeared and stayed a part of our clinical practices, at times it seems that we orthopaedic surgeons have not focused appropriate attention and/or interest on regulation. However, regulation has focused on us, and the Food and Drug Administration (FDA) has made it clear that November 2020 is on their calendar.[1,2] In "Governmental Regulations and Increasing Food and Drug Administration Oversight of Regenerative Medicine Products: What's New in 2020?"[3] Fang and Vangsness have done an excellent job providing an overview of the regulation system and recent precedent. It is important for clinicians who dive deeply into the orthobiologic space to dive deeper into the regulation space for themselves to develop a clear, personal understanding. Opinions on regulation are ever-evolving, variable, and at times industry-biased because FDA guidance and the code of federal regulation are a lot like tax code, i.e., subject to interpretation. We and/or our accountant can read the code and file our taxes however we want, but we are the ones at risk.

The FDA takes a tiered, risk-based approach to regulation. They move most quickly when it is evident that the public is at a clear risk (such as people going blind from having fat injected into their eyes), and they move slowly when it is not as evident that there is clear risk (such as people injecting bone marrow and fat into knees). This is similar to how the Federal Aviation Administration (FAA) regulates air traffic. The FAA draws clear lines, through the Code of Federal Regulations (CFRs), and takes swift actions (scrambling F-16 jets) when situations are high risk. For example, if you were to fly a small airplane into Washington, DC, you would not be in the air long. However, the FAA gives guidance and take less action in lower-risk situations. For example, if you fly a small airplane to a rural airport, FAA guidance documents outline how you "should" land your airplane there, but no jets are scrambled if you don't. The FAA is regulating in both situations but in different methods, CFRs and guidance. The FDA works the same way, with CFRs imposing strict oversight for clearly risky situations (manufacturing drugs or culturing cells) and providing guidance for less-risky situations. Just as pilots are expected to read and implement CFRs and guidance documents so that everyone is operating in a consistent, safe, and effective fashion in the piloting community, medical practitioners

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working with biologic products are expected to read and implement guidance from the FDA into their practices so that they are keeping their patients safe and treating them with effective practices and products.

3 Points

Number 1: The FDA really just cares about safety and efficacy; perhaps we should too! The mandated responsibility of the FDA is to ensure that drugs/biologics have been proven safe and effective before they are marketed. Although this slows clinical implantation of potentially effective technologies, it also forces technologies to prove their value before they become widespread, a double-edged sword.

Number 2: The FDA is effectively transmitting communications to both industry and clinicians, regardless of whether those transmissions are being received. Read their communications and determine for yourself what they mean for your practice! If you are going to read one, make it the 2017 "Guidance Documents on Minimal Manipulation and Homologous Use." It gives explicit examples regarding what to think about adipose and amnion products. This document figuratively set the table for their future actions in November 2020.[2] While these documents are readily available to medical clinicians, they are also readily available to patients and personal injury lawyers.

FDA communications available online:

- The Code of Federal Regulations (a bore to read);
- Approvals (boring but interesting precedent);
- Guidance Documents (the best and intended for both industry and clinicians);
- Untitled and Warning Letters (precedent on what not to do and lessons learned);
- Statements from the Commissioner ("Big Statements," as Dr. Andrews would say); and
- Public Safety Notifications (the FDA alerting the public to concerns about us).

Number 3: "Cleared by the FDA" may not mean what you think it means. A good example is the 510k process. The 510k process is a premarket notification of intent to market a device that companies make to the FDA through the Center for Devices and Radiological Health. If their device is determined to be substantially equivalent to legally marketed predicate devices, then a company can market their device for certain indications (which the company fills into the form). That is not the same as providing data to the FDA that a device can effectively and safely produce a product or an effect that treats an indication. With this in mind, read 510ks and remember that there are 6 centers of the FDA (the Center for Devices and Radiological Health regulates devices and the Center for Biologics Evaluation and Research regulates biologics), and a positive communication from one center does not mean that another center is okay with a proposed action. This is a point made over and over again in warning letters and equivalency documents. A common statement in their communications: "*Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies.*"

Although regulation is overwhelming at first glance and involves language that is not our typical vernacular, clinicians must understand it to effectively translate biologic technologies from interesting concepts to evidence-based medicine. The more one learns about the devil in these details, the more one is armed with an understanding of what is appropriately expected by the FDA.

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