Since our 2018 year-end post on the busy FDA regulatory agenda, we are nearing the halfway mark of the “grace period” the Agency has extended for certain regenerative medicine product developers to come into compliance by obtaining investigational new drug applications (INDs) and working towards premarket approval of their products. Recent public statements by FDA officials reiterating the upcoming November 2020 deadline have been coupled with new enforcement action or announcements about additional regulatory guidance for the industry; those two sides of the coin comprise the complementary prongs of a Comprehensive Regenerative Medicine Policy Framework rolled out by former FDA Commissioner Scott Gottlieb in late 2017. Given the number of developments in the regenerative medicine and stem cell therapy space in the past several months, it is a good time to update our readers who are interested in this exciting and transformative medical field.
Increased Regulatory Guidance for Legitimate Product Developers

First, on January 15, 2019, Dr. Gottlieb and Director of the FDA Center for Biologics Research and Evaluation (CBER), Dr. Peter Marks, released a press announcement (Link) providing a preview of additional areas FDA intends to focus its guidance development work in the year 2019. Following up on the slew of gene therapy-focused draft guidance issued in mid-2018 (see prior post here), which are expected to be finalized later this year, they promised new regulatory guidance aimed at promoting the efficient development of safe and effective cell-based therapy products. Another guideline that should be forthcoming from CBER is a recommendation for developing innovative clinical trial designs that will allow individual regenerative medicine researchers to pool their clinical data as long as they follow a common manufacturing protocol, thereby affording them the opportunity of submitting those data together to support approval of a Biologics License Application for their products. The FDA leaders noted that they “already have consortiums of academic investigators who are in active discussions with the FDA about this proposed new approach” and that the guidance document will clearly outline how this unique approach would work procedurally.

Further to the goal of developing guidance on how to implement manufacturing advancements in the cell and gene therapy fields, CBER also intends to convene a public meeting to discuss manufacturing challenges, how to collect the scientific data necessary to support moderate changes to certain processes, and where to draw the lines around what represents a minor vs a moderate or major change to cell culture methods or other production-related processes. (To date, this CBER public meeting on regenerative medicine manufacturing issues has not been scheduled.)

Next, on February 15, 2019, FDA finalized two guidance documents related to regenerative medicine therapies and specifically the Regenerative Medicine Advanced Therapy (RMAT) designation program created with passage of the 21st Century Cures Act. The first final guidance, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, describes the expedited program available to sponsors of regenerative medicine therapies and makes clear that gene therapies that lead to a sustained effect on cells or tissues are eligible for the RMAT designation (Link). The second document, Evaluation of Devices Used with Regenerative Medicine Advanced Therapies, clarifies how the Agency will evaluate devices used in conjunction with an RMAT-designated product (Link).

It is also worth updating the number of RMAT designation requests that have been granted by FDA – at the end of October, there were 26 granted RMATs. Now, as of March 31, 2019, that figure has increased to 33 granted RMAT designations (although 53 such requests have been denied and 5 have been withdrawn); 6 requests are pending as of the date of this post.

Increased Enforcement Against “Bad Actors” in the Cell Therapy Space

In the January 2019 press release, Dr. Gottlieb and Dr. Marks also noted FDA’s continued concern with individuals developing products outside of regulatory
compliance; they reported that many of those have failed to respond to the FDA’s request from November 2017 to begin a dialogue with the Agency about how to come into compliance. As a consequence, there has been a push to increase enforcement activities in this area, including from members of the Legislative Branch. The FDA leadership duo added that, in some cases, those cell therapies that are being manufactured and administered to patients are creating significant safety concerns for patients that will be driving additional enforcement actions. The focus on the most high-risk operations and those with reported serious adverse events makes sense in light of the large number of non-compliant stem cell clinics and individuals and the finite Agency resources available to conduct inspections and issue Warning Letters (or support federal lawsuits seeking permanent injunctions).

Subsequently, on April 3, 2019, Dr. Gottlieb and Dr. Marks released a statement staying true to their January 2019 promises (Link). The statement acknowledged that there has been sluggish progress by industry in coming into compliance with FDA’s regulations for human cellular and tissue-based products. As this grace period for FDA to exercise its enforcement discretion nears the halfway point (as noted above, it ends in November 2020), FDA explained that it may provide a shortcut for products that pose a lower risk to patients and that are being developed by sponsors who have engaged the regulatory process in a responsible manner by filing INDs. Additionally, FDA also acknowledged again the challenges smaller entities such as academic institutions and group practices face with product development. Drs. Gottlieb and Marks stated that the Agency would be exploring whether there are other ways to assist legitimate developers of stem cell products to come into compliance.

However, for sponsors whose stem cell products create a more significant potential risk and who have yet to engage the regulatory process to properly develop these products, the Agency’s statements and actions are becoming more pointed and direct. The April 3rd statement, among other strongly worded paragraphs, asserted:

[S]ome actors are leveraging the widespread belief in the eventual promise of these products, flouting the statutes and our regulations, and deceiving patients by illegally manufacturing or selling purported therapies, and falsely promoting their benefits. This ultimately puts at risk the very patients they claim to want to help.

It is clear that FDA will be increasing its oversight in the regenerative medicine space. To prove that point, to date, the Agency has issued at least 5 Warning Letters and has sent many manufacturers and health care providers regulatory correspondence highlighting the legal requirements for their products; 20 more of those “it has come to our attention” letters were distributed on April 3, 2019, the date of the press release. Additionally, as mentioned in a previous post, FDA has two pending court cases against stem cell clinics. It is also important to take note of the fact that the Federal Trade Commission (FTC) took its first enforcement action in late 2018 against a stem cell clinical and its operator for claiming they could cure a myriad of serious diseases. Those claims were false in that they were not supported by scientific evidence and thus were deceptive in violation of Section 5 of the FTC Act. A similar false advertising/fraud lawsuit was filed in early April 2019 by the New York Attorney General against a stem cell clinic operating in Manhattan.
This slew of activity demonstrates FDA’s – and other federal and state agencies’ –
continuing concerns regarding the numerous clinics across the country that continue
to offer unapproved stem cell products. It also reiterates that FDA intends to
continue to conduct inspections to ensure compliance and affirms that FDA will not
shy away from taking action against bad actors, while at the same time advancing
policies, programs, and public initiatives aimed at supporting legitimate product
development. The Agency has made it a point to let industry know that it can “walk
and chew gum” at the same time, and for those of us watching evolution of the
Comprehensive Regenerative Medicine Policy Framework, all of these are positive
and important steps to ensure the success of the cellular and gene therapy
industries.

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