

**FDA Media Briefing on FDA's Comprehensive Policy Framework for the Development of
Regenerative Medicine Products
November 16, 2017
11 a.m. EDT**

Coordinator: Welcome, and thank you for standing by. At this time, all participants are on listen only mode until the question and answer session of today's conference. At that time, you may press star one on your phone to ask a question.

I'd like to inform all parties that today's conference is being recorded. If you have any objections you may disconnect at this time. And now I'd like to turn the conference over to the Andrea Fischer. Thank you. You may begin.

Andrea Fischer: Good morning. And thank you for participating in today's call. My name is Andrea Fischer and I am with the FDA's Office of Media Affairs. This is a media briefing to announce the FDA's comprehensive policy framework for the development and oversight of regenerative medicine products, including novel cellular therapies.

By now, the agency's newest release and Commissioner statement for this announcement have been issued and posted on the FDA's website. Today, I'm joined by Commissioner Scott Gottlieb and Dr. Peter Marks, Director of the FDA's Center for Biologics Evaluation and Research. Commissioner Gottlieb and Dr. Marks will provide remarks on today's announcement.

Following their remarks, we will move to the question and answer portion of the call. Reporters will be in a listen only mode until we open the call for questions. When asking a question, please state your name and affiliation. Also, please limit yourself to one question and one follow-up so we can get to ask many questions as possible. I will now turn the call over to Commissioner Gottlieb.

Commissioner Scott Gottlieb: Thank you for joining us today on what is an important announcement for the agency following up on some statements we had made earlier in the year with respect to our intention to try to put forward a comprehensive framework with respect to cell based regenerative medicine. At the same time, as many of you will recall, we took some enforcement actions.

We believe this is one of the most promising areas of science. The area of cell based therapies and their use in regenerative medicine, these technologies at least in our view, most of which are in the early stages of development, hold transformative potential for patients and for the practice of medicine.

Given this area's rapid growth, its dynamism, its complexity, the field also presents unique challenges to researchers, to healthcare providers and especially to FDA. We need to make sure as an agency that we're providing a clear efficient pathway for product developers while also making sure that we meet our obligations to help ensure the safety and efficacy of these medical products so that patients can benefit from novel treatments.

To achieve these goals, today, we're taking steps to advance a new framework for how we intend to apply the existing laws and regulations. And these are laws and regulations that are already in place that govern these products. We're articulating how we intend to apply those in a modern way with this new guidance that we're issuing today.

Our aim is to make sure that we're being nimble and creative when it comes to fostering innovation. While also taking steps to protect the safety of patients. FDA, as many of you know, originally established a regulatory

framework for these products that went into effect in 2005, in regulation we implemented that year.

But in the last decade, we've seen improbable advances that hold out great hope for patients. I believe with the ability to facilitate the regeneration of parts of the human body, we're bearing witness to the beginning of a real paradigm shift in the practice of medicine.

But, that rapid growth and the promise of the field has increasingly sowed the ground for the entry of some unscrupulous actors. Some of whom we took action against earlier this year. Who, opportunistically seize upon the potential of regenerative medicine to make sometimes deceptive claims to patients about unproven and in some cases dangerous products.

By exploiting the lack of consumer understanding in this area as well as the fear and uncertainties posed by the diseases that these bad actors claim to treat, they're jeopardizing the legitimacy and the advancement of this entire field. And this underscores the importance of having clear regulatory frameworks in place for product developers, and ensuring that those who skirt the regulations are held accountable.

So, to realize the full potential of regenerative medicine, we need to support the innovation pursued by responsible product developers who represent the vast majority of the field. Help ensure that they clearly understand where the regulatory lines are drawn.

We must advance a modern, efficient, and least burdensome framework that recognizes the break neck speed of advancement and the products we're being asked to evaluate while also ensuring patient safety. And, that's the goal of the combined policies that we're announcing today. To achieve this balance

embedded in our comprehensive framework are many proposed novel and modern approaches to regulation.

Where we intend to adapt or regulatory model to meet the meet the revolutionary nature of the products we're being asked to evaluate. One example I point you to is where we're considering, how we're considering innovative trial designs.

Where academic investigators who follow the same manufacturing protocols and share combined clinical trials, can share combined clinical trial data, in support of approvals from the FDA and gain individual FDA licenses at their individual sites. There are other similarly proposed novel approaches embedded in our policy framework.

Our goal is to achieve a risk based and science based approach to support innovative product development while clarifying FDA's authority and enforcement priorities. Making sure we're protecting patients. This suite of guidances also includes other elements. It includes the implementation of the regenerative medicine advanced therapy designation program and draft guidance as well as other provisions.

We know that there's going to be questions and it will take time for product developers to determine whether their products require FDA approval. So, our policy is going to allow product manufacturers that time, through an extended period of enforcement discretion, to engage with the FDA to determine if they need to submit a marketing authorization application.

And if so, seek the guidance of the agency on how to submit their application. The exception is going to be in cases where we believe there are products that put patients at eminent risk. Where we will be taking immediate steps to

continue to enforce in this space. And we anticipate taking additional enforcement actions in the near future.

To be clear, we remain committed to ensuring that patients have access to safe and effective regenerative medication products as efficiently as possible. We're also committed to making sure that we take action against products being unlawfully marketed that pose a potential significant risk to patient safety.

The framework we're announcing today gives us a solid platform that we need to continue to take enforcement action against a small number of clearly unscrupulous factors. While making sure we have the framework in place to continue to allow good products, promising products to develop in an efficient fashion.

And so, with this balanced approach, we're well positioned we believe to support and help advance breakthrough science. Like regenerative medicine. And promote responsible and flexible regulation that leverages science to advance public health. And with that I'd like to turn it over to the Director of Center of Biologics, Dr. Peter Marks.

Dr. Peter Marks: Thanks, Dr. Gottlieb. As Dr. Gottlieb noted, the goal of releasing this suite of guidance documents is to clarify existing regulations in order to make it simpler for sponsors to develop premarket authorization, if needed, for products and to expedite the development and approval of innovative and safe, effective regeneration therapies and associated devices.

To put this in context, I'd like to take a few minutes to provide some background on the regulatory framework for these products. The laws applicable to the regulation of human cells, tissues, and cellular and tissue

based products, which I'll abbreviate as HCTPs. Include sections 351 and 361 of the public health service act.

Regulations for applying these two sections of the public health service act, HCTPs, went into effect in 2005. And, at that time, two regulatory tiers were established in the code of federal regulations. The 21CFR 1271. Those two tiers or are products that are regulated as drugs, devices and or biologic products under both sections 351 and 361 of the public health service act.

And those that are regulated solely under the authority of section 361. The products that are regulated under both sections generally involve significant manufacturing and require clinical trials to demonstrate safety and efficacy.

Whereas, products regulated solely under section 361 undergo minimal manufacturing and can be assumed to be safe and effective, provided appropriate provisions are followed to prevent the transmission of communicable diseases. So, I'd like to summarize each of the four guidance documents, starting with the two final guidances.

The document on the same surgical procedure exception, finalizes the draft guidance on this topic and addresses what types of procedures are generally considered to be the same surgical procedure and what processing steps can be undertaken to still meet the exceptions.

An example of a situation in which this guidance would apply, is when a piece of the skull is removed for decompression following traumatic head injury. The bone may be minimally processed, stored, and then returned to the individual a few weeks later when the acute event is over.

The final guidance on the regulatory considerations for human cells, tissues, and cellular and tissue based products help stakeholders understand the minimum manipulation of homologues use criterial for the development of HCTPs.

The guidance provides FDA's interpretation of the existing regulatory definitions of minimum manipulation and homologous use and consolidates and finalizes information from three separate previously issued guidance documents on minimum manipulation homologous use and adipose tissue into one document.

The guidance contains definition of key terms. Clarifies that at minimum manipulation homologous use are distinct concepts and knows how to determine if an HCTP is minimally manipulated or is intended for homologous use. A number of practical examples are provided. And, we also note that adipose tissue is a structural tissue for the purpose of the regulatory framework.

The guidance also describes the compliance and enforcement policy that the agency intends to use for HCTPs. Although the regulations regarding HCTPs have been in effect for over a decade, the level of clarity provided by the two final guidance documents may cause reconsideration of the regulatory pathway that many sponsors thought applicable to their products.

Therefore, for the first 36 months following issuance of the final guidance, FDA intends to exercise enforcement discretion for certain products that pose a low risk to public health in order to allow sponsors to have a dialogue with the agency, and, if necessary, file the appropriate regulator documentation as soon as feasible to allow sufficient time for the application process.

However, FDA does not intend to exercise such enforcement discretion for those products that pose potential significant safety concerns. For those regulatory actions related to products with routes of administration associated with a higher risk such as those administered by intravenous injection or infusion. By aerosolized inhalation, interocular injection, or injection or infusion into the central nervous system we will prioritize enforcement actions over those associated with a lower risk such as those administered by intradermal, subcutaneous or interarticular injections.

So, now I'll turn to the file, to the two drafts guidance documents. The draft guidance on the evaluation of devices used in regenerative medicine advanced therapies is required by the 21st Century Cures Act. And, when finalized, will provide a comprehensive resource to develop devices used for regenerative medicine advanced therapies, which I'll abbreviate as RMATs.

The topics covered in the draft guidance include how FDA intends to simplify and streamline its application of regulatory requirements for device and cell tissue combination products. Considerations regarding which intended uses or specific attributes would result in a device used in RMAT classified as a class III device.

When a device may be limited to a specific intended use with only one type of cell, and application of the least burdensome approach to the demonstration of how a device may be used with more than one cell type.

Finally, the expedited programs for regenerative medicine therapies for serious conditions draft guidance provides information about the expedited programs that may be available to regenerative medicine advanced therapies including fast track designation, breakthrough therapy designation. It also describes FDA's considerations in the development of regenerative medicine

therapies and opportunities for sponsors of such products to interact with agency review staff.

The RMAT designation potentially applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products and combination products. It should be noted that gene therapies including genetically modified cellular therapies producing durable effects, these may be eligible for the designation.

For a product to be eligible for the RMAT designation, it must be intended for serious or life-threatening conditions and preliminary clinical evidence must indicate the potential for the therapy to address unmet medical needs. Similar to breakthrough designation, RMAT designation provides sponsors with increased interactions with the FDA.

As appropriate, RMAT designated products may also be eligible for priority review and accelerated approval. In addition, if a designated product receives designated approval, 21st Century Cures statute provides that post approval requirements for accelerated approval may be fulfilled as appropriate through submission of clinical evidence, clinical studies, patient registries, or other sources of real world evidence such as electronic health records through the collection of larger confirmatory data sets as agreed upon with the agency.

Or, through post approval monitoring of all patients treated prior to approval of a therapy. That's a somewhat wider definition of the conventional accelerated approval, post approval requirement, fulfillment language. In addition, this draft guidance describes novel pathways for the collaboration in the conduct of clinical trials that may be appropriate for each individual investigator used to obtain biologic licenses.

So, to conclude, the suite of four guidance documents should provide those working in the field with needed clarity on those products that do and do not require premarket review.

For those products that do require premarket review, the framework includes a description of the potential pathways available to expedite the development of innovative, safe, and effective products that should be of benefit to individual and small groups of investigators. And, the guidance should also be applicable and of benefit for traditional manufacturers as well. I'll now turn the call back over to Andrea. Thank you.

Andrea Fischer: Thank you Dr. Marks. At this time, we will begin the question and the answer portion of the briefing. When asking a question, please remember to state your name and affiliation. Also, please limit yourself to one question and one follow up, so we can get to as many questions as possible. Operator, we'll take the first question.

Coordinator: Thank you. We'll now begin the question and answer session. If you'd like to ask a question, please press star one on your phone and record your name clearly. If you need to withdraw your question, press star two. Again, to ask a question, please press star one. It will take a few moments for the questions to come by. Please stand by. Our first question is from Jeneen. Go ahead. Your line is open.

Jeneen: Two questions. One, I'm hoping you can elaborate on how the agency will go about determining what products qualify as risk. Particularly in regards to adipose tissue and fat stem cell injection which are being used for so many different things.

And, my second question is, what will they be, what will you guys be empowered to do, in case it's like the ones we saw earlier this year for example, the one where the three women's vision was seriously harmed at the stem cell clinic in Florida. Will enforcement be able to go beyond warning notices and advance to something like facility closure. And that's it. Thank you.

Dr. Peter Marks: So, this is Peter Marks. So, the guidance documents explain how we treat adipose tissue. And, it distinguishes between when adipose tissue is used for structural purposes. Versus when it's used to derive stem cells. And it helps clarify situations which adipose derived stem cells would be regulated under different pathways.

In other words, under the pathways that requires biologics licensure as opposed to the one that simply requires, that does not require premarket authorization. Because, only communicable diseases have to be prevented. So, we think the guidances will help clarify that and allow us to take the enforcement actions that we need to against clinics that are, potentially, purveying dangerous products.

And, we are able, and I can't speak about any specific enforcement actions. But, in addition to untitled letters, warning letters, we can, when necessary, undertake seizures or ask for injunctions. And, in some cases, when it's been determined that certain violations have occurred, even criminal actions can be taken. So, we intend to use the full range of enforcement provisions provided to us in order to make sure that bad actors do not continue doing what they're doing.

Andrea Fischer: Thank you. Operator, we'll take the next question.

Coordinator: Just as a reminder, please say your first and last name and identify the outlet that you're with. Our next question is from (Matt Peroni). Go ahead, your line is open.

Matt Perrone: Hi guys. I'm just wondering if there was some, you know, as part of this guidance, was there any sort of economic impact assessment? Just curious, I mean, everyone knows that there's so many hundreds of these adipose stem cell clinics that have cropped up. Just wondering, you know, if we can say anything about how that's going to change that landscape.

Dr. Peter Marks: You know, we'll have to get back to you on a formal economic impact. But, I just need to make the following statement regarding that. You know, these clinics that have cropped up. There are some that are potentially actually providing bonified treatments.

And we want these guidances to help facilitate both that are providing bonified treatments, a clear path that they are operating within the law. On the other hand, what's very important is that we'll be able to undertake appropriate enforcement actions to prevent purveyors of therapies that are potentially harming people from continuing to do so.

Matt Perrone: And, do you have any plans for, you know, sort of publicizing, educating, reaching out. These are obviously, many of them, private practitioners who haven't previously thought of themselves as, you know, in the FDA sphere.

Dr. Peter Marks: It's a great question and I'm glad you asked it. By, hopefully by later today or by tomorrow at the latest. There will be a webinar that will appear, a link will appear on our website with the guidances. It's a presentation which in more detail goes through the guidances and goes into some of the depth.

Orients, it will orient a provider who is not familiar with these guidances, or even with FDA to the background of how these products are regulation and where to look for, within the guidances for the appropriate information.

Commissioner Gottlieb: Matt, I would just say, this is Scott. I would just add that, you know, there's a lot of practitioners engaging in activities that are perceived to fall within the scope of regenerative medicine. But, a lot of them are just using cells for orthopedic procedures., where they're not using homologous cells, blood cells.

Where they're not undertaking any manipulation of those cells that would put them into a regulated area. And I think what this guidance is going to do is provide clarity around what that line is and what constitutes more than minimal manipulation consistent with the regulation that's already there.

But, there's probably some ambiguity in the broader community and among even people who watch this space about what is and isn't minimal manipulation. So, to your point that there's all these practitioners out there who are now going to find themselves regulated.

I think, what we're going to find is a lot of practitioners out there who are doing things that they might be calling regenerative medicine. Really are just, using cells and not manipulating them in any way that would subject them to regulation. Peter can follow up on that.

Dr. Peter Marks: I think I just also say that in some cases, although it sounds under this rubric of stem cell therapy, some people are not even administering stem cells. They're administering mature blood cells in plasma. Which is a bonified thing that can be done.

And these guidances actually make it very clear that those are not considered. The - that's essentially something, it's a product called Platelet Rich Plasma. That that product is not an HCTP regulated under this specific framework.

Matt Perrone: Okay.

Andrea Fischer: Operator, we'll take the next question.

Coordinator: The next question is from (Murray McCullough) from the Philadelphia Inquirer. Go ahead, your line is open.

Marie McCullough: Hello. I would like to ask a question about the issue of misleading, deceptive marketing of low risk products. These products would meet the new criteria. The thing is there are hundreds if not thousands of stem cell therapy purveyors who are touting these low risk therapies as miracle cures for orthopedic problems.

And they are charging tens or thousands of dollars. Often the marketing targets the elderly. I'm wondering why the new rules don't say anything about this problem?

Commissioner Gottlieb: Well, the new rules are not necessarily silent to - the new guidance is not necessarily silent to that, the issue you're raising. The issue around, you know, deceptive promotion, we have other regulations and guidance that reach those issues.

And so, wouldn't necessarily need to be specifically called out in this guidance document which is addressing more of the scientific principals interpreting the existing regulation like what constitutes more than minimal manipulation. I mean, the purpose of this guidance is different.

The issues around inappropriate and deceptive promotion are addressed in many other aspects of FDA's regulatory architecture. And, as I said at the outset, and as Peter reinforced, we are going to be looking to take additional enforcement actions in this space. We're going to be risk based in how we apply our own resources to make sure we're getting the most bang for our regulatory buck in terms of achieving consumer protection.

And so, we're going to be prioritizing places where we see products not just being promoted inappropriately, but putting patients at potential risk. Which, that, you know, there are a suite of those that we're going to be looking at in the very near future.

Marie McCullough: Okay. Thank you.

Andrea Fischer: Okay, operator. We'll take the next question.

Coordinator: Our next question is from (Andrew Joseph) from STAT. Go ahead. Your line is open.

Andrew Joseph: Hey, thanks so much for hosting the call and taking my question. I also have a question about enforcement action. I guess it was in August, the action that you all took, I think a lot of the experts sort of applauded that. But they noted that it was, in a way, focused on sort of the worst actors, you know, the clinic that has harmed patients in a widely publicized way. And so, are the future actions you're talking about going to be going after clinics to are shown to kind of harm people, or will be a sort of broader anticipatory action?

Dr. Peter Marks: You know, we appreciate your interest in the compliance actions. The problem is we can't talk about ongoing compliance actions and I really can't

speaking a whole lot about ones that we intend to take except to reinforce what we say in the guidance that we'll take a risk based approach and that clinics that are, that happen to be using these products in a way that they are potentially treating serious or life-threatening illnesses and using these products where they are injecting them into the central nervous system or intravenously, that enforcement in those areas will be prioritized over those that are doing things that are, we perceive and are generally considered to be lower risk.

Such as, when they're being injected subcutaneously that is beneath the skin or into the joint. That's not to say that we don't care about those, it's just that, I think as the previous questioner very rightly stated, there are literally hundreds and hundreds of these clinics. And, it's very hard, we simply don't have the bandwidth to go after all at once.

So, we have to make a judgment and the judgment here is to go after the ones that are potentially harming. Where we have documented instances of harm. As again, another questioner already noted on the line, there are some very well documented, published in scientific literature even in New England Journal of Medicine instances of stem cell harm that we prioritize those actions first.

Andrew Joseph: Thank you.

Andrea Fischer: All right. Operator. We'll take the next question.

Coordinator: Our next question is from (Denis). Go ahead. Your line is open.

Denise Grady: This is Denise Grad) from the New York Times. Is that?

Andrea Fischer: We can here you.

Denise Grady: Okay. I wasn't sure that was me.

Andrea Fischer: No problem.

Denise Grady: Okay. I thought it was someone else. Okay. If you could just clarify please what you were just talking about. You mentioned the orthopedic procedures that are so common in these adipose stem cell clinics. It sounds like you're saying that, for now at least, those are okay.

Those are a lower priority because they're injecting into the joints rather than subcutaneously, or, I mean, rather than intravenously or into the nervous system. So, all this orthopedic stuff of the fat cells being spun down and then injected into knees and shoulders, that's going to be left alone right now?

Dr. Peter Marks: You know, I can't comment on what our exact specific enforcement strategy. And, I can't say that we're going to leave anything alone necessarily because it will depend on the exact circumstances. When we say prioritize, we're talking about general nature.

And the guidance talks about the general nature. I could say, also make a general statement that we're not going to turn a blind eye to a manufacturer of stem cells for injection into the knee who might be making contaminated cells that also puts people at risk.

So, I don't think it's fair to say that we're going to give anyone a free pass to do as they want. It's simply that in the scheme of things we have tiers that we will be looking at to prioritize things over. That doesn't mean we're going to ignore any part of the field.

Denise Grady: Okay.

Andrea Fischer: All right. Thank you. Operator, I think we have time for one more question.

Coordinator: Our next question is from Lynn Peterso), go ahead. Your line's open.

Lynne Peterson: Hi. This is Lynne Peterson from Trends in Medicine. So, is this mostly clinics and doctors as opposed to companies? What does this mean for companies that are actually developing products.

Dr. Peter Marks: So, for companies that are actually developing products, we actually think this is going to be very helpful. Because, we believe that it makes very clear the resources that we have in the forward direction.

Things that, how they can interact with the agency to get advice and guidance on how to help move their products forward. We think it clarifies the agency's interpretation of the regulations for them. And, it should help them develop innovative products that are safe and effective in a more efficient manner.

Andrea Fischer: Thank you. Thank you again for joining us today. As a reminder, the FDA's press release and Commissioner's statement can be accessed on the FDA's website. The concludes today's media briefing. A replay will be available in about an hour and will be up for 30 days. Thank you.

Coordinator: That concludes today's conference. Thank you for participating. You may disconnect at this time.

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