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FDA CBER Webinar: Information for Practitioners — FDA's Regulatory Oversight of Regenerative Medicine Products

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MS. LORRIE MCNEILL: Good morning, everyone. Thank you for joining us for today's event about FDA's Regulatory Oversight of Regenerative Medicine Products. Today's webinar is hosted by the Center for Biologics Evaluation and Research, or CBER for short, at the U.S. Food and Drug Administration. My name is Lorrie McNeill. I'm the director of the Office of Communication, Outreach and Development at CBER, and I will also be your host for today's event.

We have a really great agenda planned for you today. In just a few moments, I'll pass it over to Dr. Peter Marks, the director of CBER, to provide opening remarks. We'll then move into a presentation about why and how FDA regulates regenerative medicine products, the proliferation of unapproved and potentially harmful products, and the important steps that FDA is taking to ensure that therapies remain safe, effective, and of high quality for everyone. Finally, we'll finish up with a Q&A discussion to answer your questions about today's webinar topic. Next slide, please.

Before we get started, I'd like to share a few notes about today's webinar. This webinar is being recorded. The recording will be posted on FDA's website in the next few days. Closed captioning for today's event is available directly in Zoom. We will have some time at the end of the presentation for questions. If you have a question, please type your question directly into the Q&A box in Zoom. The Q&A box can be found at the bottom of your Zoom window. Please note that we are unable to answer questions about specific medical conditions and diagnoses. We also cannot answer questions about the status of particular investigational products or drug applications. We do appreciate questions and comments, and we'll do our best to address as many as we can during the event. And finally, please use the chat box if you want to share a general comment or if you are experiencing technical difficulties. Next slide, please.

I'll now pass it on to Dr. Peter Marks to provide opening remarks. Dr. Marks, thanks so much for being here with us today. Over to you.

DR. PETER MARKS: Thanks so much, Lorrie. Thank you so much to everyone for joining today.

Regenerative medicine products offer incredible potential for treating unmet medical need, but that's only if the products are well developed, they're made high-quality, and if they're safe and effective. By joining today, we hope we'll be able to explain FDA's interest in ensuring that the products that come along in this space meet that and that they are able to provide the type of benefit to patients that they deserve from the medical products that are used. In particular, we also are hoping to make clear what are acceptable products and

where there are concerns about products that may not be produced consistent with our regulations, and those can potentially bring harm to individuals.

So I really appreciate everyone joining today. I think this is a great opportunity to hear about our regulatory framework, what will fall in it, and what might fall out of it. So thanks again, and I really appreciate everyone joining, and I'll turn it back over to Lorrie.

MS. MCNEILL: Thanks so much, Dr. Marks, for that introduction, which helps set the stage for the next portion of today's event. Next slide, please.

I would now like to introduce today's presenter, Melissa Mendoza, who is the acting director of the Office of Compliance and Biologics Quality at CBER. Melissa's office oversees many important functions to ensure the quality of CBER-regulated products over their entire life cycle, from premarket review and inspection to postmarket review, surveillance, inspection, and beyond.

Melissa, thanks so much for being here today to present on this important topic. And as a reminder to our attendees, we will have some time at the end of the presentation for questions. If you have a question, please type it directly into the Q&A box in Zoom, which, again, can be found at the bottom of your window. I'll now pass it over to Melissa to begin today's presentation.

MS. MELISSA MENDOZA: Thank you, Lorrie, for the introduction. Thanks to my colleague Dr. Rachael Anatol for partnering with me on this presentation and Dr. Carolyn Yong for assisting with Q&As today. Thanks to Dr. Marks, and most of all, thanks to all the virtual attendees for being here. Next slide, please.

I'll start with a road map of today's presentation. What are HCT/Ps? Human cells, tissues, and cellular and tissue-based products. What's the relevant legal authority applicable to these products? I'll talk a bit about FDA's guidances, as well as other purported regenerative medicine products. I'll turn to the regulatory requirements for biological products, touch on compliance and enforcement and various regulatory resources available to you. Next slide, please.

What are HCT/Ps? They are, by definition, articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, transfusion — transplantation — excuse me — infusion, or transfer to a human recipient. Now HCT/Ps encompass a wide variety of products: anything from bone, ligament, skin, adipose tissue, amnion or placenta to umbilical cord, hematopoietic stem/progenitor cells, stem cells, reproductive cells, and many more. The definition of HCT/P excludes certain articles. Those include blood or blood-derived products, like platelet-rich plasma and serum, or secreted or extracted human products, among others. Next slide, please.

Where does FDA's legal authority in this area come from? Well, two enabling federal statutes. Next slide, please. First is the Federal Food, Drug, and Cosmetic Act. This statute

applies to, among other things, articles regulated as drugs, including biological products, and devices. It sets forth FDA's premarketing approval and authorization requirements, and it prohibits certain acts, called prohibited acts, and it allows FDA to pursue enforcement action, civil or criminal, through the Department of Justice. Next slide, please.

The second enabling statute is the Public Health Service Act. The Public Health Service Act applies to articles regulated as biological products. Now, as I just mentioned, the Federal Food, Drug, and Cosmetic Act also applies to biological products, because products that meet the definition of a biological product under the Public Health Service Act also meet the definition of drug and/or device as defined under the Federal Food, Drug, and Cosmetic Act. The Public Health Service Act gives FDA authority to make and enforce regulations to prevent introduction, transmission, or spread of communicable diseases. It is from that authority that FDA promulgated its regulations at 21 C.F.R., the Code of Federal Regulations, Part 1271, applicable to human cells, tissues, and cellular and tissue-based products, HCT/Ps. Next slide, please.

Part 1271 and the regulations provided there — they provide the criteria for how an HCT/P is regulated. These regulations specify that there are two tiers of HCT/Ps. In one tier, there are those HCT/Ps that are regulated solely under Section 361 of the Public Health Service Act. Those HCT/Ps are also subject to regulation under Part 1271, all the requirements therein. Importantly, these HCT/Ps do not require FDA premarket review or approval, which means they can be marketed and made available as long as they meet the regulatory requirements in Part 1271, including the criteria that we'll discuss today.

The other tier of HCT/Ps are regulated as drugs, devices, and/or biological products. The products that are in this bucket are regulated under both Section 361 and Section 351 of the Public Health Service Act; they're regulated under the Federal Food, Drug and Cosmetic Act; and they have to adhere to the requirements in 21 C.F.R. 1271, those HCT/P regulations. These HCT/Ps, like other drugs, devices, and biological products — they require FDA premarket review and approval. That means they can't be marketed until they have an approved license application, and prior to that, they can only be made available under an active Investigational New Drug Application, an IND, or an investigational device exemption, an IDE.

It's important to note that the Part 1271 regulations became fully effective May 5th — May 25th — excuse me — 2005. So FDA has had regulatory authority over these products for more than 15 years, and we know that it takes time to develop regulations, so our jurisdiction in this area was underway for at least 20 years. Next slide, please.

So what tier does any given HCT/P fall into? The regulations at C.F.R. 1271.10 specify four criteria that an HCT/P must meet to be regulated solely under Section 361. The HCT/P must be, first, minimally manipulated; second, intended for homologous use only; third, not combined with another article, and that's subject to some exceptions; and fourth, it's a bit of a mouthful, but it cannot have a systemic effect or be dependent on the metabolic

activity of living cells for its primary function, except if it's an autologous product intended for use in a first- or second-degree blood relative or for reproductive use.

Here I'd like to note a misconception. We sometimes hear or we may often hear that a product, because it's autologous, it's a 361 HCT/P, or it's not regulated by FDA at all, and this is all not true. Autologous HCT/Ps, of course, are those that are removed from an individual and implanted back into that same individual. An HCT/P must meet all four of the criteria shown on this slide to be regulated solely under 361 of the Public Health Service Act and FDA's Part 1271 regulation. That's whether the article is autologous or allogeneic. Next slide, please.

The regulations also specify limited situations in which an HCT/P establishment is not required to comply with the Part 1271 regulations at all. I'll only touch on one of these exceptions today, and that is the same surgical procedure exception outlined in 21 C.F.R. 1271.15(b). This exception states that an establishment is not required to comply with the Part 1271 requirements or with Part 1271 if it removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure. Next slide, please.

You might be thinking, "How do I know what 'such HCT/P' means? What is manipulation, what's homologous use, as applied to my specific product?" You wouldn't be alone if you feel that way. The regulations of Part 1271 set up a self-determination process. That means that manufacturers, tissue banks, establishments are charged with determining whether and what tier an HCT/P falls into and whether or not it qualifies for the same surgical procedure exception or any of the other exceptions.

Over the years, we've received questions from stakeholders asking for assistance to make this determination, and for this reason, we published two final guidances in 2017. Next slide, please.

The HCT/P guidances provide clarity to sponsors as they determine how their HCT/P is appropriately regulated.

The first guidance deals specifically with the same surgical procedure exception, and the second covers two of the four criteria mentioned earlier: minimal manipulation and homologous use. We focus on these topics in the guidances because we have received more questions about same surgical procedure, minimal manipulation, and homologous use, so we wanted to provide our current thinking and examples that might be helpful to those stakeholders. Next slide, please.

So let's start with the same surgical procedure exception. The guidance is in a Q&A format and addresses a variety of questions and products, and is meant to provide examples of the types of products and scenarios that we've been seeing. This slide covers the three elements that an establishment must meet in order to qualify for the same surgical procedure exception: The HCT/P must be for autologous use, it must be removed and

implanted within the same surgical procedure, and the HCT/P must remain such HCT/P — that is, be in its original form. Next slide, please.

"Such HCT/P" means that the HCT/P remains in its original form. The guidance explains that to remain in its original form, the HCT/P can only be rinsed, cleansed, sized, or shaped, and illustrates this through a variety of examples. Next slide, please.

Turning to the minimal manipulation and homologous use guidance, this guidance provides recommendations for applying the criteria, like 1271.10(a)(1) and (2), minimal manipulation and homologous use. It clarifies that minimal manipulation and homologous use are distinct concepts and not to be conflated. It explains how to determine if an HCT/P is minimally manipulated, how to determine if an HCT/P is for homologous use only. It also included a compliance and enforcement policy for certain HCT/Ps. I'm not going to get into that further, as that policy ended in May — at the end of May of 2021. Next slide, please.

One question we used to receive frequently was how to apply the exception at 1271.15(b), the same surgical procedure exception, and those criteria at 1271.10. This diagram/flowchart was intended to walk through this whole analysis. You first ask if your product is an HCT/P. If it is, you then determine if it meets any of the exceptions in 1271.15. If it does not, then you move on to evaluate the four criteria in 1271.10(a). Next slide, please.

So turning to minimal manipulation, the regulations lay out two separate definitions of minimal manipulation. One is for structural tissues, and one is for cells and nonstructural tissues. There are a few things to keep in mind when evaluating the minimal manipulation criteria. First, it's important to remember that this criterion relates to how the HCT/P functioned in the donor. You have to evaluate all the processing steps that are applied to that HCT/P, and you have to begin the analysis with the HCT/P as it existed in the donor.

This means that you look at the processing from start to finish and determine whether or not the processing alters the tissue's utility in the donor. Has the tissue lost its ability to function as it did in the donor? If so, we would consider that tissue, for example, to be more than minimally manipulated. Next slide, please.

Let's take the example of amniotic membrane. The utility of amniotic membrane in the donor is to serve as a barrier. If you process amniotic membrane into a sheet form, you have not altered the amniotic membrane's relevant characteristics related to its utility to serve as a barrier. In sheet form, amniotic membrane retains its utility to cover. That amniotic membrane would not be more than minimally manipulated. Conversely, if you process amniotic membrane into particulates, for example, that processing alters the utility of the amniotic membrane to serve as a barrier, and we would consider that processing to be more than minimally manipulated. Next slide, please.

And what about adipose tissue? Adipose tissue's utility in the donor is to provide cushioning and support. If you process adipose tissue to remove the adipocytes and you leave behind the extracellular matrix, you alter the tissue's utility to provide cushioning and support. That adipose tissue would be more than minimally manipulated. Likewise, if you process adipose tissue to isolate stromal vascular fraction, or SVF, you alter the tissue's utility to provide cushioning and support. In both of these examples, we consider the processing to be more than minimal manipulation of the adipose tissue. On that basis alone, the adipose tissue, the HCT/P, would not meet all the criteria of Part 1271.10(a) and would be regulated under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act as a drug and biological product. Next slide, please.

We could go over many more examples, but I will move on to homologous use. The homologous use criterion states that an HCT/P must be intended for homologous use only, as indicated by the manufacturer's intent. The regulations define homologous use as the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. If the HCT/P is intended for use as an unproven treatment for a myriad of diseases or conditions, the HCT/P is likely not intended for homologous use only. Next slide, please. Actually, could we go back to the last slide? Thank you.

I didn't note the bold text in the last bullet, but please keep in mind that the homologous use criterion relates to the intended use of the HCT/P in the recipient. That's an important concept to keep in mind. Thank you. Next slide, please.

For amniotic membrane, when it's intended to be used as a cover in the recipient, we consider that to be homologous use, because serving as a cover is a basic function of amniotic membrane in the donor. However, if amniotic membrane is intended to be used to replace bone and support bone regeneration, we consider this to be a nonhomologous use, because bone regeneration is not a basic function of amniotic membrane.

Now speaking to the clinical effects, the guidance describes that wound healing, a reduction in scarring or inflammation, those are not homologous uses of amniotic membrane. Some preclinical studies, we acknowledge, have demonstrated that amniotic membrane may be able to reduce scarring and inflammation, but these are not well understood and accepted basic functions of amniotic membrane, so we don't consider them to be homologous use. Next slide, please.

Hematopoietic progenitor cells, as we know, can be obtained from bone marrow, the peripheral blood system, or blood. When HPCs are used to replenish the bone marrow, we consider this to be homologous use. However, if HPCs are intended to be used for the treatment of, for example, cerebral palsy, we would consider this to be nonhomologous use. Again, the nonhomologous use — the homologous use criterion is one of those criteria at 1271.10(a), and failure to meet that criterion alone is reason for the article to be regulated as a drug, device, and/or biological product. Next slide, please.

Moving on to other purported regenerative medicine products, ones that we're seeing more and more, and unfortunately, many that are being marketed unlawfully — next slide, please — one of these products is exosomes. Exosomes are regulated by FDA. To be clear, as a general matter, exosome products intended to treat diseases or conditions in humans require FDA approval. There are currently no FDA-approved exosome products, and exosome products may only be distributed to participating investigators and/or administered to humans if a sponsor has an Investigational New Drug application in effect, an IND.

We're also seeing a lot of Wharton's jelly or Wharton's jelly-derived products. This — Wharton's jelly is regulated by FDA as a drug and biological product and also requires FDA review and approval. We often see Wharton's jelly products marketed as 361 HCT/Ps, and the same really applies to exosomes. That is not correct. Again, these products are marketed — are regulated as drugs and biological products. Next slide, please.

We're also seeing a lot of amniotic fluid unlawfully marketed. Amniotic fluid is considered to be a secreted or extracted human product, and therefore it does not meet the definition of an HCT/P. So instead, amniotic fluid is regulated as a drug, device, and/or biological product, depending on factors such as its intended use. But to be clear, because amniotic fluid is not an HCT/P, we do not apply the criteria of 1271.10(a) to amniotic fluid products. We do, however, often see amniotic fluid referred to as a 361 HCT/P. Again, that is not true, and any such marketing would be false, as well as misleading. Next slide, please.

On to the regulatory requirements for biological products. Next slide, please. So many of the products that we're discussing today, when they don't meet the criteria at 1271.10(a), many do meet the definition of a biological product under the Public Health Service Act.

So what are those requirements for biological products? To lawfully market a drug that's also a biological product, a valid biologics license must be in effect. Such licenses are issued only after a demonstration that the product is safe, pure, and potent. Again, in the investigational stage, prior to approval of a biologics license for commercial distribution, these products can only be distributed to participating investigators and/or administered to humans if a sponsor has an Investigational New Drug application in effect. Registration in eHCTERs — that's our online registration and listing system for HCT/Ps under Part 1271 — that does not mean that a product or establishment is in compliance with FDA regulations. Firms can register and list, unfortunately, even if they inappropriately determine that their product is a 361 HCT/P. But again, that does not mean that the establishment or the product is in compliance with FDA regulations. Next slide, please.

To this end, we're aware of products being unlawfully marketed and made available to patients illegally, and when we are, we take action. But we learn a lot about — a lot of this information from you, from stakeholders, from concerned patients, and we want to hear from you. This information is extremely helpful to us. It sometimes fills in the gaps of information that we have and we've been able to obtain. So please, even if you think that

FDA must know about the availability of a certain product that you believe may be marketed unlawfully, if you believe that there's an establishment that's not operating within the confines of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and the Part 1271 regulations, please, let us know. You may submit a complaint. But also know that we, unfortunately, cannot provide updates on the status of your complaint or share the information about the investigatory work of the agency in response. Next slide, please.

Let me tell you a little bit about our enforcement efforts; that, as I think is clear from this presentation, we acknowledge that there are manufacturers, distributors, health care providers who are continuing to market unapproved regenerative medicine products to patients.

These products have risks that are not just theoretical, and they need to be demonstrated to be safe and effective before they can be used on patients. They need to be appropriately studied under an IDE or through — through an IND or an IDE. And we have — and like I said, these products come with safety concerns, and we've shared publicly that these types of products may present risks — and have, in certain instances — of blindness, tumor formation, neurological events, bacterial infections, unwanted inflammatory or immune response, and many more. Next slide, please.

So one thing that we can do is pursue enforcement action, and we have done so through the U.S. Department of Justice, which, on our behalf, has filed injunctions seeking to cease the manufacturing and distribution of unlawful products, including cellular products derived from adipose tissue as well as other culture or cellular products. We also have the authority to seize products through our seizure authority under the Federal Food, Drug, and Cosmetic Act. We have seized ACAM 2000 back in 2018. That ACAM 2000 was being combined with stromal vascular fraction derived from adipose tissue and used to treat advanced-stage cancer patients. Next slide, please.

Another thing that we can do and have done regularly is issue warning letters, untitled letters, or send other letters putting firms on notice. All of our warning letters are available online, and they provide a great opportunity to see trends in the Agency's compliance and potentially what may turn into enforcement. You can filter by the issuing office, and I have that information available on the slide here, so you can readily access warning letters for these products and filter those out from the various other FDA commodities.

We can also issue untitled letters. Likewise, untitled letters put firms on notice of their violations of the law, just like warning letters. Usually we're issuing untitled letters when we have not conducted an FDA inspection of the facility or in other circumstances where, for example, we may only have website claims and other information and not the benefit, like I said, of a facility inspection in order to put a firm on notice of its violations.

We've also issued hundreds of "It Has Come to Our Attention" letters. These letters are not compliance actions. They're more so communications to establishments and manufacturers when we become aware of information that may be concerning about that establishment's regenerative medicine product. We use these letters to ensure that these establishments and manufacturers and health care providers know that they are on FDA's radar, that we're aware of certain information about them, and that we encourage them to engage with the Agency on the regulation of their products, as well as the HCT/P framework. Next slide, please.

You should know that, increasingly, states are now pursuing their own actions. So we're pleased to say and know that FDA is no longer alone in trying to combat and curtail the problem of unapproved regenerative products being marketed and available throughout the country. Some states that have been actively involved — and there are many more than this — but New York, Georgia, Iowa, Nebraska, Washington. If you're interested, you may want to look into all the various actions taken in those states and what they're doing to help, again, address this problem. Next slide, please.

Moving on to some FDA resources available to you — next slide, please — so, as I mentioned earlier, the process for determining whether and how an HCT/P is regulated is really left up to the establishment. It's a self-determination process as to whether or not that HCT/P is regulated under Section 361 of the Public Health Service Act and the regulations at Part 1271 solely, or whether that product does not meet any of the criteria of 21 C.F.R. Part 1271.10(a) and is therefore regulated as a drug, a device, and/or a biological product.

However, establishments should not feel alone in making this determination, because FDA has many resources available to manufacturers and establishments to opine in various different ways, formally and informally, on the regulatory status and classification of any HCT/P. So informally, manufacturers can reach out to the Tissue Reference Group, the TRG. That's through the TRG, manufacturers can obtain an agency recommendation on the regulatory status of the HCT/P. More formally, these manufacturers can go and seek an RFD, a Request for Designation. Now this is a formal agency designation through FDA's Office of Combination Products on the regulatory status and classification of the article, the HCT/P.

And even — another option is a pre-RFD. And that is, prior to getting an RFD, manufacturers or establishments can seek preliminary feedback from the same Office of Combination Products on the classification of an HCT/P. In addition, many establishments and manufacturers have contacted both OTAT, our Office of Tissues and Advanced Therapies, as well as OCOD, our Office of Communications, Outreach and Development, to ask questions, and all those questions get answered. So once again, there's — no one is in the dark as to how their product is regulated, and FDA has an abundant number of resources available to all interested. Next slide, please.

So what else can FDA do about concerning products? We can post consumer warnings and other notices, and we certainly have, as reflected on this slide. We've done this for the HCT/Ps that are being unlawfully marketed to patients, especially for a wide variety of diseases or conditions. We've issued alerts for exosomes in particular, consumer updates. And we know that different messaging resonates differently with various stakeholders, that — we've found some of these products available to be so troubling that we've posted on our website a consumer alert, which has been received well. It essentially states that stem cell products, exosomes, Wharton's jelly, amniotic fluids, stromal vascular fraction, all of them — none of them, I should say, have been approved for the treatment of, for example, COVID-19, orthopedic conditions, neurological disorders, cardiovascular or pulmonary diseases, or other conditions, such as autism, fatigue, chronic pain, despite what you may see online or what a health care practitioner or establishment may be marketing its products for.

A reminder: I know I've said it so many times at this point, but these products for these uses are regulated by FDA as drugs and biological products, typically, and require our premarket review and approval. Next slide, please.

So a recommendation that we have for patients: Patients who are considering treatment with any HCT/P or purported regenerative medicine product should ask if the FDA has reviewed the treatment, ask for the FDA-issued IND number, and ask to review the FDA communication acknowledging the IND — again, one example of what patients can do, and there's no reason that this information cannot be provided to a patient. Next slide, please.

This slide includes a number of regulatory resources. If you have questions about the IND requirements for any of these products, there's an email address for the Office of Tissues and Advanced Therapies, and they can walk you through those requirements. OTAT also has a "Learn" series that you can access at the website provided. There are guidances on cellular and gene therapies, there are the tissue guidances that I mentioned, and there's a listing — importantly, there's a listing of FDA-licensed cell and gene therapy products. So we do get a lot of questions about whether or not a particular product is licensed, and so going to this website is a very helpful resource. Next slide, please.

This is the contact information for OTAT. Oh, sorry. One back. Yes, thank you. Contact information for OTAT. Please use it. OTAT is extremely responsive and is always answering questions and helping with the IND requirements as well as others. Again, the webinar series is available at that link. Next slide, please.

And this is the CBER contact information. Yes. The Office of Communications, Outreach and Development is extremely responsive and answers questions all the time. And every day we see patients and others contacting OCOD with questions, and they are — they diligently respond both on the phone and in writing to any questions that may arise.

I mentioned earlier that if you have concerns, complaints, information you just want to bring to the attention of the Agency, we really welcome that information. We use it. It's very, very helpful to us. Please provide that to OCOD at the various different email addresses provided here. Next slide, please.

Well, thank you. I really appreciate you all listening in today, and Dr. Yong and I are available for questions.

MS. MCNEILL: Thanks so much, Melissa, for your presentation today.

We'll now move on to the Q&A discussion. I'd like to take a moment to introduce Dr. Carolyn Yong, who's joined us today to help answer your questions. Carolyn is the associate director for policy in the Office of Tissues and Advanced Therapies here in CBER. Carolyn, thanks so much for being here today.

As a reminder to our attendees, we will try to address as many questions as possible, but please remember we are not able to discuss questions regarding specific investigational products or marketing applications. We did receive a number of questions when folks registered for the event, so we'll start off with those today. Our first question is for Melissa. Do you have any comments on the Cell Surgical ruling — Cell Surgical Network ruling that took place in August?

MS. MENDOZA: Thanks, Lorrie, and thanks for this question, a very important one. I cannot, like any other FDA representative, speak to or comment on the Cell Surgical Network decision or litigation, as with any pending litigation. I will, however, direct the questioner to the U.S. Department of Justice, specifically the Appellate Division, for any additional information.

MS. MCNEILL: Thank you, Melissa.

Our next question is for Carolyn. Is there a listing of all the FDA-approved regenerative medicine products that are on the market?

DR. CAROLYN YONG: Yes, the publicly available FDA website has a web page dedicated to the listing of approved cellular and gene therapy products. Also, one can query the publicly available FDA medical device databases for approved or cleared medical devices. And you know, I'd just like to add that registration of a particular device establishment or assignment of a registration number, you know, listing of a medical device wouldn't in any way denote that approval of the establishment or its products by the FDA.

MS. MCNEILL: Thank you, Carolyn.

Melissa, you just talked a little bit about how people can provide information to FDA, including complaints. Can you explain other ways that FDA becomes aware of illegal products and if there are any steps taken prior to issuing warning letters?

MS. MENDOZA: Yes, there are many steps taken and many avenues for us to receive that information. Separate and apart from complaints and other inquiries, we conduct inspections. Our Office of Biological Products Operations conducts inspections on our behalf of various facilities and establishments, because if those facilities and establishments are not registered with us — let's say maybe appropriately or inappropriately — under the Part 1271 regulations, we still have authority to go out and inspect. And so we may issue directed inspection assignments, and we have issued many of those. Inspections are obviously the ways in which we can obtain the most information about any particular manufacturer or establishment. But we have many other means of obtaining information: Through our state and federal counterparts, there are a lot of information sharing mechanisms, and as I — we receive MedWatch reports and other information about adverse events, and I encourage the submission of any of that type of information as well. Once again, from complaints and inquiries and any sort of reporting of possible adverse events that, like I said, may help fill in gaps in information that we have or kind of lead us in a direction as to where to go inspect or look next. So those, just to name a few, Lorrie, are the ways in which we obtain information and what we do with that information, such as conduct inspections.

We also have our own Internet surveillance efforts and other efforts, and work with others in the public sector, such as large retailers and marketplaces, where some of these products may be available — so again, so many different ways in which we try to combat this problem and things that we may do well in advance of an inspection and well in advance of a warning letter. So when you see that warning letter, a lot of investigational work likely has gone into it, above and beyond just the inspection that's referenced.

MS. MCNEILL: Thank you for that explanation.

Carolyn, the next question is for you. Platelet-rich plasma, which is also known as PRP, is not considered an HCT/P because it's a blood product. However, in addition to platelet concentrates intended for transfusion, PRP is widely used for regenerative medicine and often prepared with nonconforming devices — for example, tubes that are intended for in vitro diagnostic purposes or kits registered with FDA under an incorrect classification. What are the regulations that apply for the preparation of this product?

DR. YONG: Right. So platelet-rich plasma, or PRP, which is blood taken from an individual and given back to the same individual as platelet-rich plasma, is not an HCT/P under Part 1271, because it is a blood product. Blood products are outside the scope of the presentation in today's webinar, but questions about specific products and their intended use are certainly welcome and may be submitted to us.

MS. MCNEILL: Thank you for that.

Melissa, next question for you: Are vendors liable for inaccurate or unsupportive regenerative claims or false advertising?

MS. MENDOZA: Yes. So vendors would be — let's say who are offering these products — would be liable for making them available, for the marketing of them, for the distribution of them, as would — and for receiving those products in interstate commerce, for example, just as the manufacturers would be liable under the Federal Food, Drug, and Cosmetic Act or, rather than liable, I should say subject to potential compliance and enforcement action.

Earlier in the presentation I had mentioned the prohibited acts that the Federal Food, Drug, and Cosmetic Act outlines, and those prohibited acts are — that's the basis and what we use to move forward with enforcement action. Those prohibited acts are drafted, fortunately for us, broadly to include both the conduct — I should say the conduct and the actions of those throughout the chain of commerce. And so that would cover, again, the manufacturers, the vendors, and even distributors of these products.

MS. MCNEILL: Thank you for that.

Carolyn, next question for you: Google, for some time now, has eliminated the ability to do ad campaigns and remove sites from searches using their search engine for the use of terms such as PRP, regenerative medicine, et cetera. Is there a way to educate these Internet companies as to what is or is not appropriate language?

DR. YONG: Well, I'd certainly like to thank our stakeholders for this comment. This sort of activity is outside of our purview. However, the Agency certainly encourages actions in the interest of public health and that are taken to protect consumers.

MS. MCNEILL: Thank you.

Melissa, next question for you: How is FDA addressing the bad actors and stem cell clinics that offer these unapproved regenerative medicine therapies?

MS. MENDOZA: Thanks, Lorrie, and thanks to the questioner. We've done a lot in this space, we continue to do a lot of work, and we encourage any input on what more we can do within our authorities. So for one, we have used our authority and the tools that we have to combat this problem. As I mentioned, we have pursued and, at the appellate level, we've prevailed in enforcement actions involving cellular products that are marketed unlawfully. This includes the DC Circuit and the 11th Circuit Court of Appeals in the cases of the United States versus Regenerative Sciences and the United States versus US Stem Cell.

As I mentioned, FDA inspects — whether or not these establishments put themselves on our radar, we find out about them, we conduct inspections, and, based on all the other information noted earlier and ways in which we get information, we determine whether those establishments are violating the law, and we put them on notice through those various communications, warning letters, untitled letters that I mentioned. Those are the precursors to potential enforcement action. So they're very helpful — not necessary, but very helpful, to hopefully — which is our goal — curtail the problem and achieve voluntary compliance in the industry.

I will say that we have had a number of successes in this area by issuing warning letters. You'll note — or if anyone is interested to look back at our compliance actions — even from the end of the compliance and enforcement policy that I had mentioned ended last year, at the end of warning letters, you will see that firms have made a lot of commitments to cease distribution and cease marketing — not all, so we still have — for the ones that we've attempted to address, we still have problems on our hands and more work to be done, but we are seeing more voluntary compliance than we had seen in the past, and so that is promising. But again, much more work to be done, but that's how we've used our authorities.

We've also — as I said earlier, we've used our voice as a public health authority, getting the word out to — through our various consumer statements on our website, informing stakeholders of the warning letters that we issue in the hope that they will have a deterrent effect is another way to go about trying to address the problem.

I mentioned earlier too that the Office of Communications and OTAT and others at CBER and FDA respond to questions every day and speak to patients directly and try to advise them of the risks and the concerns that FDA has. So that's also a very important way that — ways we are trying to address that problem. But — and two more things: We obviously partner with our state and federal counterparts, sharing information, and we've had our state partners embargo products, which is a great authority and work that we hope to continue to collaborate with those state partners on.

And lastly — and I really do mean it — if there are other actions that FDA can take that anyone on this call or any stakeholders have, we always welcome that information, and we encourage it to be submitted to us and suggested to us.

MS. MCNEILL: Thanks so much for that, Melissa.

Carolyn, next question for you: Is cord blood an HCT/P?

DR. YONG: Cord blood, a source of hematopoietic progenitor cells, or HPCs, is an HCT/P.

MS. MCNEILL: Thank you. One more for you: So based on the flowchart that Melissa presented during her talk, if an establishment is under the same surgical procedure exception, and this is an upstream of all other criteria of HCT/Ps regulated under 361, can the establishment use the cells if they are more than minimally manipulated without going through the HCT/P 351 path, such as gene-modify them while they are in an apheresis collection bag?

DR. YONG: Well, why don't we unpack that question a little bit? The Agency is certainly happy to clarify the same surgical procedure exception for our stakeholders. So for the same surgical procedure exception to apply, you know, the subject HCT/P needs to be autologous and implanted within the same surgical procedure. And a key point is the HCT/P must remain, quote/unquote, "such HCT/P," meaning it should be in its original

form. So, as Melissa pointed out in her presentation, generally the only processing steps that would allow an HCT/P to remain "such HCT/P" are processing steps such as rinsing, cleansing, sizing, and shaping. In general, processing that would be considered more than minimal manipulation would not allow an HCT/P to be "such HCT/P." And you know, generally speaking, HCT/Ps that are genetically modified would not be considered "such HCT/P."

MS. MCNEILL: Thank you for that explanation.

Melissa, our last question is for you. Is there a way that the public and medical community can report clinics who are unlawfully selling HCT/Ps for unapproved uses?

MS. MENDOZA: Yes, and please do. So the contact information for — CBER contact information slide that I shared earlier has various email addresses. Please reach out to any of the contacts there and inform us of any information that you may have about clinics that are unlawfully marketing their products. Yes, that slide. Don't hesitate to call. Don't hesitate to email. There will always be someone available to take this information and route it appropriately.

Again, I mentioned this earlier, but it bears repeating: You may think that FDA must know about a particular establishment or clinic or product. Still, submit it. It's extremely helpful to us — and any additional information you may have. We do have a lot of health care practitioners contact us for advice or assistance — I mentioned patients, but health care practitioners as well — and they put a lot of different clinics and products on our radar or, again, further supplement information that we may already have. So thank you in advance, for asking the question and for submitting any information you may have to OCOD.

MS. MCNEILL: Thank you so much, Melissa and Carolyn, for answering all our questions today and participating. I'd like to thank everyone who joined for attending today's event. As a reminder, a recording will be posted on FDA.gov in the coming days. On this slide, you'll see resources for more information to stay up to date on the latest announcements of events from CBER. So you can visit the CBER website, sign up for our "What's New at CBER" listserv newsletter, you can follow us on Twitter @FDACBER, or visit some of the helpful resources that are listed on this slide. Thank you again for joining. I hope everyone has a good day.